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THE IDENTIFICATION OF TUMOR CELLS IN SEDIMENTS OF SEROUS EFFUSIONS *

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Microscopic examination of sediments from aspirated effusions, chiefly those of pleural or peritoneal origin, has proved to be a useful procedure in the clinical diagnosis of primary and metastatic malignant tumors of the membranes of these cavities. As such examinations frequently cause considerable discussion and offer many difficulties in the way of exact diagnosis, the following paper is presented in an attempt to evaluate our criteria for judging whether or not cells of malignant tumors are present in a given specimen. In our experience these examinations have been of most value in connection with exudates from the pleura, pericardium and peritoneum; gastric contents, sputa and the like have not proved to be favorable material on account of the mucous content, the paucity of cells in a given sample, and so on. As Graham [1] has reported in a similar article, many hospital pathologists have resorted to essentially the same technique for treating and examining these sediments, devising their methods quite independently of one another; probably the first to publish such a procedure was Mandlebaum [2] in 1917. Smears of fluid sediments have been examined since the earliest days of pathology; Zemansky [3] gives an excellent review of the history of this technique. Four articles have recently appeared on the examination of smears stained in various ways, the most modern employing vital, or supravital technique. These papers are by Quensel,[4,5] Karp,[6] and Merklen, Waitz and Kabaker [7]: the first two will be re-

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ferred to later on. Merklen, Waitz and Kabaker have published an excellent study of the cytological varieties and peculiarities of cells found in serous effusions, illustrated by a large colored plate that is valuable as an atlas to those inexperienced in the examination of these fluids.

The method devised by Mandlebaum consists of allowing the specimen to settle somewhat, decanting the supernatant fluid and centrifugating the residue until a small button forms at the bottom of the tube. This is then isolated by pouring off the fluid and replacing it with fixing solution which shrinks the button and separates it from the glass. It is then removed and cut in two vertically, so that its section surface represents all the layers of the centrifugate. It is then embedded in paraffin. Any fixing fluid may be used and the sections cut from the button may be stained as desired. During the past 3 years we have used essentially the same technique. If the amount of fluid be small, it is immediately centrifugated; if there be a large quantity enough glacial acetic acid is added to bring the acid percentage up to about 2 per cent (20–30 cc. per liter). This is stirred in and prevents the coagulation that ruins one's chances of obtaining a good sediment; it also lakes the excess of erythrocytes and thus rids the sediment of much confusing detail. The fluid is set in the ice-box overnight, the clear supernatant fluid decanted, and the cloudy residue is centrifugated until the button is well formed. Our routine fixative for this is 10 per cent formalin in 95 per cent alcohol. Mandlebaum's method of bisecting the button vertically is good in theory, but in practice we have found that it tends to crumble to bits during the process and that it is better to embed it on its side and cut well into it on the microtome before taking off paraffin sections. These are best stained by Masson's trichrome light green method, which gives excellent details and usually stains the nucleoli vermillion with the ponceau, so that they are readily identified and measured. The same dye is excellent for demonstrating intercellular bridges, which is often of diagnostic advantage. Any other stain is, of course, applicable.

Zemansky has established some criteria for judging the presence or absence of tumor cells in a given fluid. He states that tumor may be suspected when one finds: (1) fragments of tissue with definite arrangement of cells and stroma, such as acini or papillae; (2) multiple groups of large, deeply staining cells, giving the section a

mottled appearance; and (3) finer cellular changes, such as extreme irregularity of cell outline, eccentricity of nucleus, extremely large size of nucleus, multinucleation and typical or atypical mitotic figures. He believes that it is all-important to know the duration of the effusion and the history of the case, as the longer the duration the more atypical will be the cells observed. He has not found mitotic figures in fluids not showing tumor cells, although he notes that Dock reported finding them. His review of the accuracy of the method, as checked by autopsy and biopsy at the Mount Sinai Hospital in New York over a period of many years, shows that the percentage of correct diagnoses was 87 per cent in the case of positive fluids, and 47 per cent in that of fluids reported negative. Fluids from carcinoma cases showed cells in 60 per cent of 55, and those from sarcomas 33 per cent of the total examined. Of 35 cases of intra-abdominal neoplasm, 65 per cent showed tumor cells in the fluid, and 30 cases of intrathoracic tumor showed 50 per cent.

Curious to ascertain how correct our results might have been, I have reviewed all our material received between September 1932 and January 1936, consisting of 55 specimens of ascitic fluid and 85 of pleural effusion. Four pericardial fluids were all negative and will not be discussed. Of the pleural and ascitic fluids three patients furnished 5 specimens each, two 4, five 3 and eleven 2 apiece; the remainder furnished a single specimen each. In reviewing this admittedly small series of specimens the results obtained at the original routine examinations were collected and checked for accuracy against the respective histories, using any available data from autopsy, biopsy, operation, X-ray examination or, failing these, from the clinical history to guide us. All these sections were next examined on a purely morphological basis, without any knowledge of whence they came or what may have been the history in each case.

The first series, diagnosed by the staff and myself in collaboration, showed 62 per cent correct, 34 per cent incorrect and 4 per cent doubtful in the ascitic fluid cases; the recheck, done on a purely morphological basis, showed 72 per cent correct, 24 per cent incorrect and 4 per cent doubtful. The original reports on pleural fluids were 70 per cent correct, 26.5 per cent incorrect and 3.5 per cent doubtful; my recheck was only 65 per cent correct, 31.5 per cent incorrect and 3.5 per cent doubtful. This was largely due to extreme caution in pronouncing doubtful cells to be tumor cells.

In making the recheck each slide was examined and plus or minus signs were placed in columns under the headings "tumor," "mitoses," "multinucleation," "metaplasia," "cell clumps," and "acini or papillae." Mitoses were present in 26 per cent, multinucleation in 65 per cent, metaplasia in 43.5 per cent, clumping in 54 per cent, and acini or papillae in 15 per cent. Forty-eight cases had histories of proved carcinoma. If we check these against these headings we find that the number of examinations in which multinucleation, metaplasia and cell clumping were found exceeds the total number of proved cases (35 per cent) and that these criteria are not reliable for judging the presence or absence of tumor cells. Mesothelial cells floating in a transudate, which is apparently an excellent culture medium, multiply by mitotic division and round up and become at least anaplastic in their appearance, which is confusing. Mitoses were seen in 24 positive and 12 negative fluids, so that their value as an indication of the presence of neoplasia is about 66 per cent; atypical, or "monster" mitoses may, however, be considered to be pathognomonic of the presence of tumor cells.

Before comparing our figures with those of Zemansky, which were tabulated on a somewhat different basis, those cases not checked by anything more accurate than clinical data were discarded and the rest were then tabulated. In the original series of reports the diagnosis of ascitic fluids that should have shown tumor was 73 per cent correct; in the recheck it fell to 60 per cent. Ascitic fluids with no proof of carcinoma were correctly diagnosed in only 36 per cent of the original reports, while the recheck improved this to 75 per cent. The original diagnoses on pleural fluids from cases with proved cancer were 60 per cent; the recheck fell to 53 per cent. Pleural effusions from cancer-free cases (of which there were only 3) were correctly diagnosed in both series. Averaging these results to cover all these cases selected for comparison with Zemansky's figures, it is found that 66.5 per cent are correct in positive tumor cases and 68 per cent in tumor-free cases in the original series; in the recheck 56.6 per cent are correct in the positive and 87 per cent on the tumor-free cases. The results, then, fall far below Zemansky's 87 per cent where tumors are concerned, but lie well above them where the reports are negative, his figure being 47 per cent. Table I in the text will show a compilation of these figures, together with those obtained

TABLE I

Percentage of Correct and Incorrect Diagnoses of Presence of Tumor Cells

General Results on Entire Series (Unselected Cases)

Source	1st Examination			2nd Examination			3rd Examination		Averages		
	C	I	D	C	I	D	C	I	C	I	D
Abdominal Fluid	62	34	4	72	24	4	63	37	65.5	31.5	3
Thoracic Fluid	70	26.5	3.5	65	31.5	3.5	70	30	68.5	29.5	2

Results on Selected Cases Checked by Autopsy, Biopsy or Operation

Tumor Present											
Abdominal Fluid	73	27	0	60	40	0	72	28	69	31	0
Thoracic Fluid	60	40	0	53	47	0	81	19	65	35	0
Tumor Absent											
Abdominal Fluid	36	64	0	75	25	0	62	38	58	42	0
Thoracic Fluid	100	0	0	100	0	0	58	42	89	11	0
Average of selected series									70	30	0
Average of both series									68	30.5	1.5

C = correct; I = incorrect; D = doubtful.

when using another method of attack on the problem, which will be discussed presently.

The reason for mistakes in diagnoses of this sort is not far to seek: there are large numbers of exfoliated mesothelial cells in most fluids of long standing, whether of quasi-inflammatory origin, or provoked by the presence of tumors or their metastases. These cells often resemble those of malignant growths quite strikingly in that they present hyperchromasia, large and deeply stained nuclei and often nucleoli, are frequently multinucleated, quite often show mitotic figures, clump together to form structures much like acini and often show eccentrically placed nuclei. One or two disastrous experiences in misdiagnosing these cells as cancer cells tend to make the observer unduly cautious and pessimistic. For these reasons, Zemansky's criteria must be revised. We may accept the presence of frank tumor fragments as incontrovertible. Irregularity in the size and shape of the nucleus and the presence of large and bizarre forms or *atypical* mitotic figures are also criteria that stand confirmed.

What further data can one adduce to assist in improving one's accuracy of diagnosis in these instances? Quensel [4,5] has devoted much time to the origin of the various cell forms encountered in smears of sediments and appends a good bibliography to his copiously illustrated papers. He stresses the point that the ratio of nucleus to nucleolus is always high in cells of malignant tumors and much lower in the normal components of mesothelial or retothelial tissues. In the former it lies between 0.20 and 0.40, in the latter below 0.20. He obtains this ratio by measuring the diameters of nucleus (N) and nucleolus (n) and dividing the latter by the former. We shall speak of this ratio as the "n/N ratio" in this paper. He prefers moist smears of sediments stained supravitally with methylene blue cadmium or Sudan III cadmium, but has also used Giemsa's and Ehrlich's triacid stains. Following his lead, Karp [6] has worked along similar lines and confirmed Quensel's findings. Believing that accuracy was to be improved by using the ratio of areas, rather than diameters, he measures the longest and shortest diameters of nucleus and nucleolus and calculates their areas from the formula for obtaining the area of an ellipse $\pi \left(\frac{d_1 + d_2}{4}\right)^2$ applied to each set of diameters. The figures thus obtained may be more

accurate but they improve the results relatively little, the process is time-consuming, and the fact that cells in fluids tend to become rounded up into spheroids makes it rather unnecessary. There are comparatively few elongated ellipsoidal cells to deal with.

Forty-four representative slides were segregated from our series and I applied Quensel's measurements and method for obtaining the n/N ratio to each, without using any other criteria whatsoever. Ten cells were measured with an ocular micrometer in each section and the diameters averaged, the n/N ratio being calculated by dividing the average nucleolar by the average nuclear measurement. The figures, obtained in fixed and embedded sediments, agree entirely with those of Quensel and of Karp and the percentage of accuracy of diagnosis arrived at by this method is surprisingly good.

It is found that in making these measurements only doubtful cells should be selected, otherwise the large number of monocytes and frankly mesothelial cells present will bring the ratio too low, where only a few tumor cells are present. A typical ascitic fluid, for example, will show a majority of cells with nucleoli too small to be accurately measured with a No. 3 ocular micrometer and a 1/12th oil immersion objective. In such cases one may be reasonably sure that no neoplastic elements are present. When, however, a small number of cells with prominent nucleoli are seen, one should measure these. One of our sections, about to be pronounced non-neoplastic, was shown to be the contrary because the doubtful cells gave a high n/N ratio. Further search revealed a large clump of typical carcinoma cells in a tumor fragment, which appeared in only one out of three serial sections.

Most of the fluids show a ratio below 0.20 when no tumor is present, but one of 0.25 to 0.40 when it is present, which is in material accord with Quensel's and Karp's figures. The disappointing feature of this method proves to be a small group of cases whose n/N ratio falls between 0.20 and 0.25, for it is just this group that causes doubt when judged on a morphological basis. The average in twenty-one sections from pleural and ascitic fluids diagnosed as tumor-positive was 0.265, the ratios running from 0.17 to 0.40; pleural effusions from 8 cases of cardiac decompensation gave an average n/N ratio of 0.204, fluctuating between 0.15 and 0.23, and the purely ascitic fluids averaged 0.207 with a low of 0.16 and a high of 0.28. Out of these 44 sections 68 per cent were correctly and 32

per cent incorrectly diagnosed by the use of the n/N ratio, which is a hopeful sign as an attempt was made to neglect morphology utterly and to rely solely on the n/N ratio.

These findings are of interest in view of what MacCarty [8, 9] has claimed for several years as to the difference in the ratio between the size of nucleus and nucleolus in cells of hyperplastic normal tissues and those of neoplasms. He has insisted on these measurements being made in fresh material stained without fixing. In his most recent paper he has tabulated the results obtained by other observers who have followed his methods and one is struck by their general agreement. These workers all use the N/n ratio, which is the reverse of that used by Quensel, Karp and myself, in that the nuclear measurements are divided by the nucleolar, the greater by the lesser. They also work on a volumetric, rather than on a diametric or areal basis, taking the longest and shortest diameters for their areal calculation and multiplying the result by the shortest diameter, on the assumption that nucleus and nucleolus have a single long diameter and two equal transverse diameters. A little calculation on the part of the reader will show that the ratios they obtain are quite similar to those arrived at in this paper. An n/N ratio of 0.15 equals an N/n ratio of 6.66, one of 0.20 (the "critical point") will be 5.0, one of 0.25 will be 4.0 and our maximum of 0.40 will become 2.5 in the N/n figures; by multiplying these N/n ratios to obtain the cubes, figures are found that tally quite closely with those in MacCarty's paper.[9] One cannot figure out the actual spheroidal volume from these diametric ratios without knowing the longest and shortest diameters, for reasons already given.

In a recent paper Guttman and Halpern [10] have reported the examination of a large number of tumor and normal hyperplastic cells in tissues fixed in Zenker's solution and stained by Pappenheim's method. Their findings prove to their satisfaction that there is no appreciable difference between the N/n ratios of these two groups. Be this as it may, the results set down in this paper would indicate strongly that there is a definite difference in the case of cells in effusions, whether fixed or unfixed tissue is examined. MacCarty makes an exception in the case of two types of cell: the oöcyte and the cells of the nervous system, such as ganglion cells. In the case of sediments from effusions it might be well to except the cells of the lymphocyte series from the general rules here set down; their

nucleoli are too inconspicuous to measure. Large numbers of these cells, however, indicate clearly enough some dyscrasia in the lymphoid system if they be predominatingly immature in their type.

It is found that the presence of "signet ring cells," stressed by some authors as indicative of neoplasia, is a relatively common finding; the vacuoles in macrophages often mislead one into mistaking them for cells of a mucous carcinoma. This doubt may be readily settled by using a mucicarmine stain, which will show mucus as a bright vermillion substance in such vacuoles. Mesothelial cells often have a peripheral border-zone of small vacuoles, or projecting serrations that suggest intercellular processes, facts that may be of help in identifying them.

Four photomicrographs have been taken to illustrate this article. Figure 1 shows a section of sediment from the pleural fluid in a case of carcinoma of the ovary; almost anyone could diagnose this correctly at a glance. Figure 2 came from the pleural fluid in a case of carcinoma of a stem bronchus with pulmonary metastasis. The clumps of large dark cells with apparently prominent nucleoli are significant, but without the n/N ratio (0.266 in this case) one might be left in doubt. In Figure 3 we have a sediment from an ascitic fluid in a case that was later examined by autopsy and no tumor was found. This case gave us much trouble as it was repeatedly reported positive for tumor on the original examination of five consecutive specimens. On the recheck, however, it was correctly diagnosed in every instance. The n/N count gave four out of five correct diagnoses, the ratio being 0.193 in the specimen illustrated, which indicates "no tumor found." As Zemansky points out, a negative diagnosis is inconclusive, as tumor might be present without any cells getting into the fluid. Here, however, autopsy showed that there was no tumor. Figure 4 is from a chest fluid from a case of cardiac decompensation with terminal pulmonary infarcts. This also gave us trouble. There are numerous large cells present, one of them showing a normal mitosis with slender chromosomes. The n/N ratio here is 0.172, which is definitely low.

Additional typical photomicrographs might have been selected for publication, but there are plenty of them in the literature; Quensel's articles have 35 plates and 74 figures which illustrate every conceivable phase of the question in excellent photomicrographs.

Summary and Conclusions

Summarizing the findings of this brief investigation we should revise the criteria for reporting "tumor cells present" in a given fluid in somewhat the following manner:

1. Zemansky's first criterion, the presence of fragments of tumor with the cells arranged in acini or papillae about a stroma that is definitely fibrovascular, stands uncontroverted.

2. A nucleolar-nuclear ratio falling above 0.25 is of undoubted value; one of 0.30 or more practically pathognomonic of the presence of tumor.

3. Mesothelial pleural, pericardial and peritoneal covering cells present the chief obstacle in the way of successful diagnosis as they are readily confused with tumor cells on account of their large size and prominent nucleus. When they are measured the dimensions are found to be quite uniform and regular; tumor cells, on the other hand, show a high n/N ratio and a wide variation in measurements.

4. Multinucleation is of no diagnostic value and cell clumping is almost as worthless. Mitosis occurs in both positive and negative sediments, but monster, or abnormal mitoses are found only in tumor cells.

5. The occurrence of erythrocytes and fibrin is of little diagnostic value.

Note: I am much indebted to Dr. Earl P. Lasher for his assistance in compiling the histories and assembling the material for study in connection with this paper, and to Miss E. Dreyfoos, of the department of photography, for the photomicrographs.

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DESCRIPTION OF PLATE

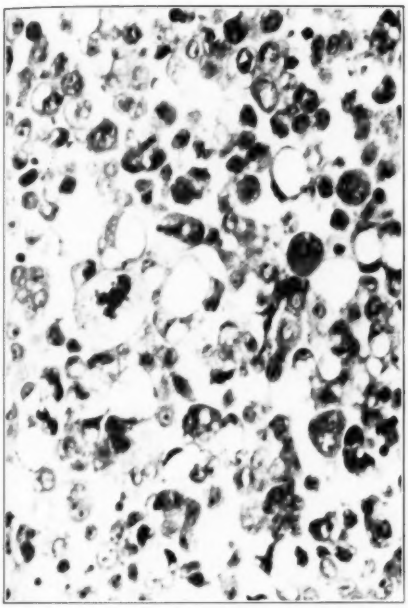
PLATE I

FIG. 1. Sediment from a chest fluid in a case of ovarian carcinoma. Note the irregularity in size and shape of the cells, the enormous mitotic figure in the center of the field and the prominent nucleoli. × 327.6.

FIG. 2. Sediment from a chest fluid from a case of main stem bronchial carcinoma with pulmonary metastases. This is much less evidently neoplastic, but the irregularity of the cells is manifest and the nucleoli are prominent. × 327.6.

FIG. 3. Sediment from ascitic fluid in a case of periportal cirrhosis of the liver. The cells are numerous, deeply staining and apparently neoplastic. Mitoses are present elsewhere in the section, not shown in this field. × 327.6.

FIG. 4. Sediment from pleural fluid in a case of decompensated heart and pulmonary infarcts. A large mesothelial cell in mitosis is shown at the center. Notice occasional clumping of the cells. × 327.6.



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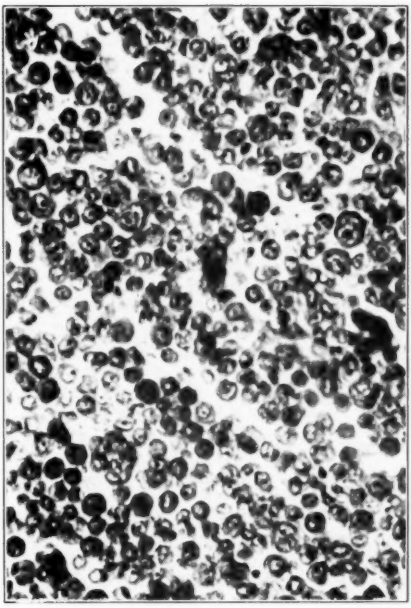

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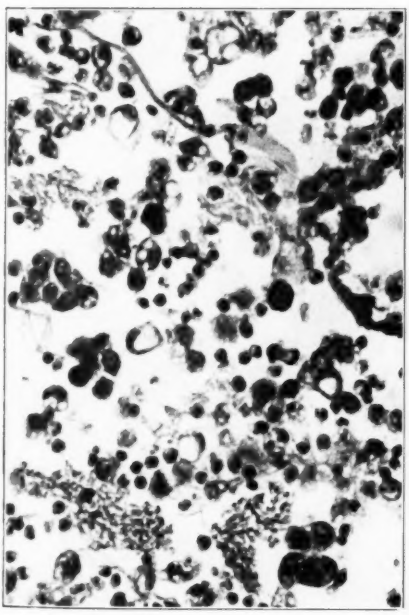

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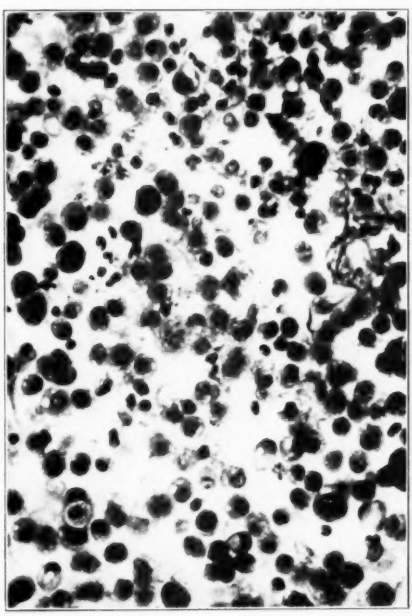

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Foot

Tumor Cells in Sediments of Serous Effusions

THE SIMILARITY OF THE LESIONS PRODUCED BY SILICA AND BY THE TUBERCLE BACILLUS *

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The lesions of silicosis and tuberculosis are essentially similar. In human cases where the two conditions are frequently associated it is often impossible to be certain of the etiology of a particular lesion. A proper diagnosis is made only on reviewing the gross appearance of the entire lung and on the examination of a number of histological sections. The lesions of experimental silicosis produced in animals by the injection or inhalation of excessive quantities of fine silica particles may even more closely resemble those of tuberculosis.

It is not the purpose of this paper to discuss the differential diagnosis between silicosis and tuberculosis but to call attention to the close similarity in the tissue response to silica and to the tubercle bacillus. It is remarkable that a simple inorganic compound such as dioxide of silicon (SiO_2) can set in motion a complicated series of cellular reactions comparable to those produced by a living organism made up of proteins, carbohydrates and lipoids. Each one of these components is customarily assigned a special rôle in the production of the tissue reaction to the tubercle bacillus. The proteins are known to stimulate exudation from the blood vessels; the lipoids, proliferation of fixed tissue elements; and the carbohydrates determine humoral changes. Furthermore, these major elements have been split into a number of chemical fractions which on injection into animals have produced either exudative or proliferative tissue responses. The validity of these observations has not been questioned, but it is at least debatable whether or not the tubercle bacillus excites a given cellular reaction because of the presence of some fatty acid that can be extracted from it by chemical manipulation.

It will be shown that silica can cause every type of cellular response found in tuberculosis. The nature of its action in the body still remains a mystery. Many observers believe that gradual solution of the mineral poisons the tissues; others think that undefined physicochemical properties of the surfaces of the silica particles may be responsible. Neither hypothesis has been proved but the fact

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remains that silica has a different effect from that of any other inorganic material that has been investigated. It sets in motion a train of cellular responses, beginning with exudation and proliferation, which may terminate with necrosis sometimes associated with calcification. It is conceivable that there are physicochemical properties, common to both silica and tubercle bacilli, that act on living cells in a similar manner. Since the nature of the injury produced by either of these irritants is still unknown, it is of interest to correlate any relevant data.

Proof of the similarity of the cellular response to silica and to the tubercle bacillus will be drawn from a series of experiments on different species of animals, birds and fish. Cats, rabbits, guinea pigs, white rats and mice, domestic fowl, gold fish and tadpoles have all reacted to silica, and some form of tubercle bacillus will also produce lesions. In some of the species it was necessary to employ subcutaneous injections but these will not be used to illustrate the subject to be discussed because of the non-specific mechanical effects that may be produced by the local introduction of great numbers of foreign particles. Inhalation and intravenous injection of dispersed suspensions of low concentration are not open to this criticism. By the latter methods the irritants establish contact with the cells at points remote from the portal of entry through more or less natural physiological processes. A sufficient concentration can be built up by repeating the injection or inhalation as frequently as necessary. The evolution of the reaction to intravenous injections of silica and aluminum oxide [1] and of that to inhaled silica [2] have been described elsewhere. References to the effects produced by the inhalation of other dusts will be found in the latter paper.

Within broad limits the character of the tissue response to the introduction of foreign particulate matter depends on the chemical composition, quantity, size and state of dispersion of the irritant. In administering living organisms such as the tubercle bacillus, only the initial quantity and their dispersion and virulence are subject to variation. Because of their capacity to multiply in the tissues, even a small dose soon becomes capable of provoking reaction. Clumps of organisms are avoided in order to prevent mechanical effects, and those associated with the introduction of excessive amounts of foreign protein. If the bacilli are dead, masses of them must be introduced to produce a tubercle. In the case of inorganic material all of

these factors must be even more carefully controlled. Chemical composition is limited to SiO_2 in this discussion, although reference will be made to other substances which serve as controls. The quantity introduced by dispersive methods such as inhalation and intravenous injection must be excessive so that enough particles will localize in different foci to produce reaction. Guinea pigs must inhale hundreds of millions of silica particles for at least 2 hours a day over a period of 5 to 6 months before significant changes begin to appear in the lungs. In the previously published intravenous experiments [1] as much as 1.3 gm. of silica containing approximately 330 billion particles, 1 to 3 μ in diameter, were injected. Subsequently it was found that 0.1 gm., or about 30 billion particles, would produce the same effect in a somewhat longer time. A dose as small as 0.05 gm. was ineffective.

Particle size is probably the most significant of all the factors as it determines the rate and severity of tissue response. Recently in this laboratory Vorwald has shown that a large fragment of quartz crystal, weighing 2.5 gm., embedded in the subcutaneous tissues of a guinea pig for 1 year stimulated the development of only a few mononuclear cells along its borders. It has been reported [1] that relatively large particles, 10 to 12 μ in diameter, provoke a foreign body type of reaction that progresses very little in a year or two, but that small particles 1 to 3 μ in diameter cause rapidly progressive tissue changes. Subsequent experiments have shown that the injection of 0.2 gm. of minute silica particles, 1 μ or less in diameter, causes even more acute reaction with death in 1 to 8 months. Gye and Purdy [3] demonstrated years ago that intravenous injection of still finer colloidal silica is almost instantly fatal. The examples cited amply demonstrate that the rate of reaction to quartz in the body is inversely proportional to the particle size.

The state of dispersion of the silica particles in air or fluid suspensions is of importance also. Clumps introduced into veins produce embolic effects and wherever they localize an abnormally acute reaction may occur. Masses of particles in the atmosphere of a dusting chamber are not readily inhaled, but when once the lungs are penetrated tissue responses quite different from those produced by gradually accumulating dust are evoked.

For these reasons the illustrations have been chosen from the lungs of guinea pigs inhaling silica for many months, and from the livers

and spleens of rabbits injected intravenously with repeated small doses of the same material. The particles accumulated in these organs gradually and their cells were never overloaded by excessive accumulations at any time. Non-specific reactions were thereby reduced to a minimum.

Wherever silica particles lodge, small mononuclear phagocytes make their appearance. In the spleens and livers of rabbits they are first seen in the sinuses and sinusoids. The free cells increase with considerable rapidity during the period of injection. Whether they continue to be poured out of the blood stream or connective tissues, or whether they multiply locally is not altogether clear. Mitotic figures are uncommon but evidence of direct nuclear division is sufficiently notable to suggest that this mechanism may be at least partially responsible The cells have an abundant pale cytoplasm, an eccentric nucleus, are ameboid and capable of ingesting either silica particles or tubercle bacilli. Given the opportunity the same cell may engulf both irritants. When stained supravitally with neutral red a majority of these cells exhibits the monocytic type of granule distribution, having a rosette of fine droplets about the centrosome in the indentation of the nucleus. Some are of the clasmatocyte type, with large, irregularly distributed droplets of dye and vacuoles containing débris of partially digested leukocytes. Silver impregnation reveals no trace of fibrils at this stage of their development. In the writer's opinion these cells should be classified as histiocytes.

The ameboid phagocyte usually carries the ingested silica particles away from the area where they first settle and deposits them in foci more removed from the functional cells of the organ. In the lungs deposition occurs in the lymphoid tissues, in the spleen in the lymph follicles, and in the liver the silica is collected in the portal connective tissues. The accumulated phagocytes form nodular masses in these locations. Some of the cells are often killed by the toxic silica they contain, in which case polymorphonuclear leukocytes are attracted. New mononuclear cells enter the area to take up the liberated particles. In the lung, supravital staining demonstrates that the phagocytes simulate epithelioid cells at this stage. Their cytoplasm contains enlarged rosettes of finely granular neutral red droplets and scattered bodies of a lipoid nature which stain with scharlach R. Similar preparations have not been made from the

spleen and liver, but there is no reason to suspect that the cells are any different in these organs.

Giant cells develop early in the tissues reacting to silica. In the lungs multinucleated forms appear in the air spaces which are indistinguishable from the cells produced by inhaled tubercle bacilli. They may have eight to ten peripherally arranged nuclei and a hypertrophied rosette of neutral red granules. Other giant cells which obviously originate from the fusion of contiguous phagocytes in which the individual small rosettes are preserved are present also. The latter are more common in silicosis than in tuberculosis. In the liver small giant cells promptly appear in the sinusoids after the injection of silica. These cells have six to eight nuclei arranged in a ring at the periphery. In their cytoplasm polarized light reveals a few silica particles but not more than four are usually seen in a section 6 μ thick. Such cells seem to be produced by direct division of the original nucleus without segmentation of the cytoplasm. In the spleen similar multinucleated cells of both types are found in the sinuses.

About 2 months after completing the injections the mononuclear phagocytes forming the nodule in the splenic follicles may be largely transformed into giant cells if the silica they contain is of the proper size. Similar forms are numerous in the lymph nodes and occur occasionally in the liver. These cells may be extremely large, measuring from 30 to 120 μ in maximum diameter. They are irregularly ovoid with a dense homogeneous, eosinophilic cytoplasm and contain twenty-five to fifty or more nuclei. The latter are arranged either about the periphery or in superimposed masses in the center of the cell. Rarely a vacuole is visible but most of the cells have none. Giant cells rarely contain more particles than the original mononuclear phagocyte. They resemble closely the Langhans' cell of tuberculosis and do not exhibit the long cytoplasmic processes seen on foreign body giant cells that develop about agar, sutures and other large insoluble materials.

Giant cell formation is in no sense specific for the reaction to fine particulate silica. Injection of 1 to 3 μ particles of various silicates, of oxides of iron, aluminum and titanium, and of silicon carbide likewise produces multinucleated cells, but they are quite different from those that have just been described. They are never as large, are more apt to be spherical, and contain such large numbers of particles

that their internal structure is completely obscured. Here and there a nucleus may be visible and an occasional droplet of neutral red can be detected in supravitally stained preparations. They have not even a superficial resemblance to the Langhans' type of cell.

Where giant cell formation does not dominate the picture, mononuclear elements still play the leading rôle in the developing nodule. In preparations stained with hematoxylin and eosin all of the cells resemble the original free phagocytes, but neutral red staining demonstrates that some of them contain only a few, fine scattered droplets of dye. Such cells are apparently fibroblasts although they have the same shape and general appearance as the epithelioid cells. Silver impregnation reveals a fine network of reticulum wound over their surfaces, which is not found on the epithelioid cells. Apparently both fibroblasts and epithelioid cells are developing in juxtaposition. If one is so inclined the evidence can be interpreted as a demonstration of transition from one to the other.

A more rapid proliferation with division by mitosis now ensues. Many of the more mature cells are pushed toward the periphery of the nodule where they become flattened and assume the characteristic spindle form of the fibroblast. The associated reticulum fibers thicken and in time take specific stains for collagen. At the center of the lesion there is a variable number of polygonal cells, most of which are of the epithelioid type. Giant cells rarely persist in the center of the silicotic nodule. They are either destroyed and replaced by fibrosis, or they remain in the foci that do not progress to this stage.

If a somewhat greater but still limited amount of silica happens to localize in an area, continued cell proliferation results in the formation of a nodule composed largely of fibroblasts. Peripheral extension and probably altered pressures tend to produce a laminated arrangement. The reticulum increases in amount and is ultimately replaced by collagen. In some instances a fiber may be stained partly brownish black by silver and partly red by the fuchsin used in Foot's modification of the Bielschowsky technique. As the collagen becomes thicker and more hyalinized it stains intensely with eosin in other stains. The cells are compressed almost beyond recognition and the nodule now assumes the characteristic appearance of the mature silicotic lesion.

Foci that contain still more silica particles undergo central degeneration. The process starts as a coagulation necrosis accom-

panied by karyolysis. Special stains disclose fat in fine droplets throughout the débris. All traces of nuclei disappear except in the immediate vicinity of larger blood vessels which are often resistant. If the injury is not too severe the reticulum also persists and with the disappearance of the cells it may be the only structure left in the center of the lesion. As it subsequently thickens and is compressed by the surrounding cells that have not been killed, the reticulum forms a compact central core in the nodule.

Excessive concentrations of finely granular silica particles produce an injury so severe that even the reticulum is destroyed and nothing but granular necrotic débris is left. Such material attracts lime salts and calcification follows. This termination has been encountered most commonly in rabbits but it has been seen in a few human cases also. The shell-like encapsulation of a central necrotic mass sometimes seen in tuberculosis is uncommon in the silicotic lesion.

At the periphery of the silicotic nodule there is a variable number of lymphocytes but they are not usually arranged in the form of a definite zone. In organs other than the spleen they may accumulate in more or less circumscribed masses at areas on the periphery of the nodule.

The same general type of reaction to intravenous injection of silica evolves in the liver, bone marrow and lymph nodes. Inhalation produces a similar picture in the lungs. Variations in the form of the lesion are produced by anatomical peculiarities of the organ concerned.

In different species of animals the reaction to silica exhibits certain variations. Rats, for example, rarely show persistent necrosis or calcification; most of the nodules are quickly transformed into a hyaline fibrosis. Rabbits develop more calcification than guinea pigs. Chickens show less tendency for the fibrous tissue to become hyaline. In the terminal lesions ordinarily seen in human beings some of the nodules may still contain necrotic centers and occasionally there is calcification or even ossification. In a few individuals dying after relatively short, intense exposures, the more acute necrotizing reactions seen in experimental animals can be discovered.

As might be anticipated, the development of a tubercle-like nodule of epithelioid cells does not of itself create skin hypersensitiveness to tuberculin. Only when the nodule is produced by tubercle bacilli

containing specific sensitizing proteins is there any skin hypersensitiveness. Early in the study of silicosis the similarity of the lesions to tubercles prompted a large series of tuberculin tests, but none of the guinea pigs reacted. Sabin, Doan and Forkner [4] had the same experience with an Aspergillus that produced pseudotubercles. Intracutaneous injection of silica into silicotic animals produces a tuberculin-like reaction with necrosis and marked hyperemia in 48 hours, but the same effect is manifested in non-silicotic controls. The inflammation is not a result of sensitization but is merely a local manifestation of the toxicity of silica.

It is not necessary to describe the comparable stages of the response to tubercle bacilli for these are too well known. Sabin, Doan and Forkner [4] have recently published an excellent review of the subject with original contributions on supravital staining. The primary mononuclear cell reacting to both silica and the tubercle bacillus is apparently the same. The two irritants seem to affect it in the same manner, producing the variations known as epithelioid and giant cells. Both agents cause exudation and necrosis of tissue with the liberation of free fat, and in each case this necrotic matter may become calcified. Both cause continued proliferation of mononuclear leukocytes and fibroblasts which are laid down in the form of a nodule. About the periphery of these nodules in each case there is a zone of lymphocytes. The elements of the tissue reaction to the tubercle bacillus and to silica are essentially identical and the resultant lesions are similar.

There are certain differences due in all probability to the nature of the two irritants. Not all silicotic nodules undergo all of the stages of evolution that have been described, for the characteristics of the reaction are determined by the local concentration and the size of the particles. A small number of coarse particles produces proliferation with little or no necrosis. Moderate concentrations of fine particles are responsible for fibrous nodules with necrotic centers. About excessive numbers of minute particles proliferation is overshadowed by degeneration and necrosis. The primary response to the tubercle bacillus is more uniform. The number of organisms that will develop in a primary tubercle after inhalation infection never exceeds a certain maximum, regardless of their virulence and the resistance of the host. Whenever bacillary multiplication becomes excessive, the lesion spreads to new areas. The rate of bac-

terial proliferation is fairly well balanced against that of the host cells. As a consequence, all primary tubercles are more or less alike: they develop in an orderly manner and exhibit quite definite zones of reaction although there are minor variations due to factors of dosage, virulence and resistance in the host. Silicotic lesions are also progressive but added reaction occurs in the immediate vicinity of the original site of localization. Particles that once become surrounded by a zone of fibrosis are not carried elsewhere unless this fibrous tissue is destroyed by inflammatory changes due in most cases to secondary bacterial infection.

Tubercles sometimes heal and leave only a fibrous nodule which may simulate the nodule of silicosis. Where this happens the fibrosis from infection is not usually as uniformly laminated nor is the collagen as heavy and hyaline in appearance. However, it should be borne in mind that pulmonary tubercles may be modified by small amounts of silica. An immobile structure in the parenchyma of the lung, such as a healed tubercle, often attracts and retains inhaled foreign material. Deposits of black carbon in the periphery of healed foci in the lungs and the tracheobronchial lymph nodes are so common that they cause no comment. Colorless silica particles may accumulate in the same locations but as they are only visualized in polarized light they frequently escape detection. The amount that is inhaled varies with the environment, but the lungs of most adults contain appreciably more than those of children. It is probable that many healed tubercles with heavy zones of hyaline fibrosis have been influenced by the silica concentrated at their periphery.

In summary, it may be affirmed that the simple inorganic substance, silicon dioxide (SiO_2), is capable of exciting every tissue response that can be produced by the complex living organism *Mycobacterium tuberculosis*. The reaction to the latter is more uniform because its constitution is more or less constant and it soon establishes a limited equilibrium with the tissues of the host. The reaction to silica is largely determined by the number and the size of the particles that come to rest within a given focus in the body. Both irritants cause varying degrees of proliferation, exudation and necrosis, resulting in a nodular type of reaction.

If one may speculate on the causes of this similarity it would seem that both irritants are relatively insoluble, but that perhaps both of them continually liberate minute amounts of irritating substances.

Exotoxins have never been demonstrated for the tubercle bacillus and the proof of solution of silica in the body is still debatable. Possibly the combined effect of mechanical irritation by the undissolved portion, and the slow but continuous elimination of irritating tissue poisons are responsible for the striking similarities.

Both irritants react on the mononuclear phagocyte to alter its internal structure in a similar manner. If the lipoid elements of the tubercle bacillus are responsible for the production of epithelioid cells it is difficult to imagine what comparable substance could be liberated from the molecule of silicon dioxide. Would it not be profitable to study the physicochemical conditions in the tissues to discover whether or not the two irritants may produce similar changes in the environment of the cells?

It has been shown that both irritants injure mononuclear phagocytes so that multinucleated giant cells are produced. The particular conditions necessary for such reaction have been examined in detail in the case of silica and the reasons for postulating a dual stimulus have been set forth. It has further been shown that mechanical stimulation alone does not produce Langhans' giant cells, and that silica produces them only when the particles are large enough to exert some mechanical effect and small enough to present a sufficient amount of active surface in contact with the cytoplasm of the phagocytes for chemical reaction to occur. It is of interest to note that this optimum size approximates that of organisms such as the tubercle bacillus which measures from 0.1 to 4 μ in diameter. The physicochemistry of the interior of living cells is largely unexplored but until further progress has been made in this field the ultimate nature of the injury caused by the tubercle bacillus and by silica will probably remain a mystery.

The nodular character of the lesions in both silicosis and tuberculosis is also probably dependent on altered behavior of the mononuclear phagocyte. In each case this cell is responsible for the concentration and the walling off of the irritant in a localized focus. The surfaces of the irritated cells seem to become viscous so that they adhere to one another, as demonstrated by free-floating tubercles in the peritoneal fluid after the local injection of bacilli. As phagocytes proliferate about a collection of particles or bacilli in the tissues they tend to remain *in situ* and form the primary nodule. The subsequent proliferation of fibroblasts contrib-

utes collagenous fibers that bind the other elements into a compact mass.

The mature fibrosis of silicosis is somewhat different from that caused either by the tubercle bacillus or by other irritants. Intercellular fibers begin to increase in number and size early in the course of the reaction. They resist the necrotizing action of the silica unless its concentration is excessive. They manifest unusual tinctorial properties with various dyes, showing a particular avidity for acid stains such as eosin. If one accept the solution hypothesis it is quite possible that the dissolved silica forms a physical or a chemical combination with collagen, which prevents its diffusion beyond the limits of the nodule. This would explain the lack of reaction in surrounding tissues and in remote excretory organs such as the kidney. Nonsilicious dust particles produce no such hyaline swelling of the collagenous fibers. In healed tubercles it is only of note in locations where inhaled silica could be attracted to the lesions.

This study has confirmed the specificity of the tuberculin reaction and has again demonstrated that the mere presence of a pseudotubercle composed of epithelioid cells does not create hypersensitiveness to tuberculin. Silica itself is not antigenic and intracutaneous injections produce the same effects in silicotic and in normal control animals.

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DESCRIPTION OF PLATES

PLATE 2

FIG. 1. Drawings of monocytic cells from silicotic and tuberculous lesions stained supravitally with neutral red. Silicotic cells on the left; tuberculous on the right.
A = an unstimulated monocyte; B and C = stimulated monocytes; D and E = epithelioid modifications; F, G, H and I = clasmatocyte types; J and K = Langhans' type giant cells with hypertrophied rosettes of neutral red granules.

FIG. 2. Proliferative silicotic nodule in lung of a white rat inhaling quartz dust for 6 months and then allowed to live in a normal atmosphere for another 4 months. Nodule is forming in lymphoid tissue associated with a small blood vessel. × 130.

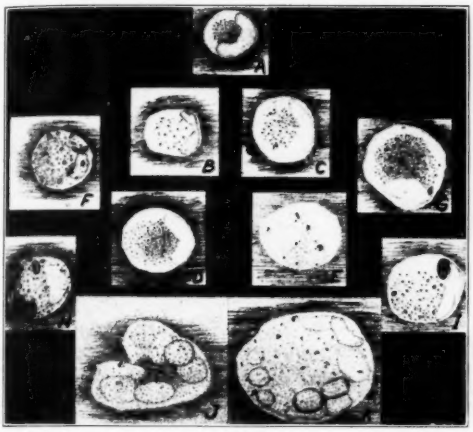
FIG. 3. Proliferative silicotic nodule in the spleen of a rabbit injected intravenously with 0.5 gm. quartz particles less than 3 μ in diameter. Administered in 20 doses over a period of 2 months. Animal killed 3 weeks after last dose. Epithelioid and giant cells show no necrosis. × 130.

FIG. 4. Minute silicotic nodule stained by Foot's method for reticulin to show the fibrils forming about the young fibroblasts. A small secondary nodule in the lung of a rabbit inhaling quartz for 13 months and then allowed to live in a normal atmosphere for another 17 months period is also seen. × 64.3.

FIG. 5. Minute tubercle, stained by Foot's method for reticulin, occurring in lung of rabbit injected subcutaneously 5 months previously with 25,000 virulent bovine tubercle bacilli. × 64.3.

FIG. 6. Langhans' giant cells in a silicotic nodule in a rabbit's spleen. Animal received same treatment as that illustrated in Fig. 3. × 64.3.

FIG. 7. Proliferative silicotic nodule in lung of a white rat. The cells resemble fibroblasts and are actively dividing. Four mitoses are seen in this field. From the same animal as Fig. 2. × 130.



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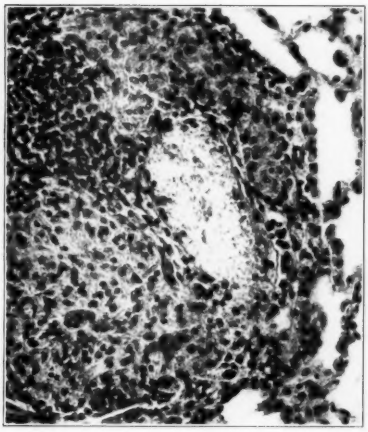

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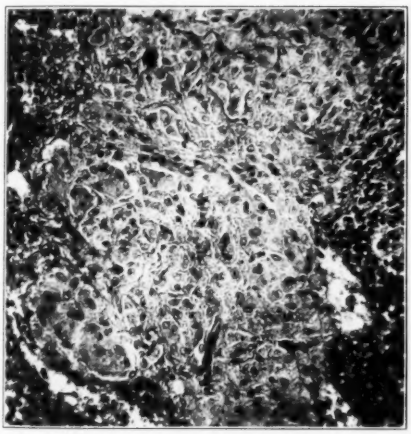

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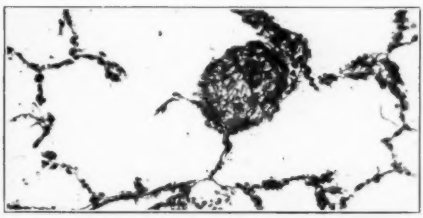

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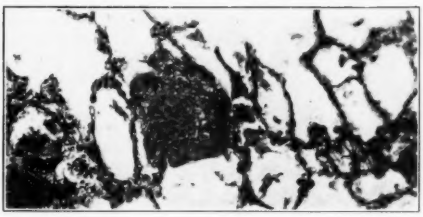

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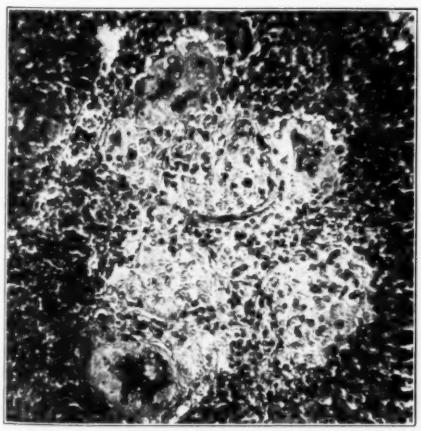

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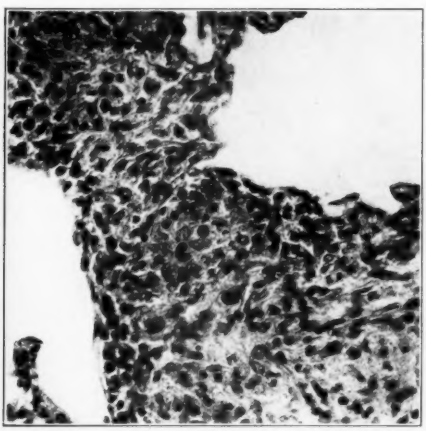

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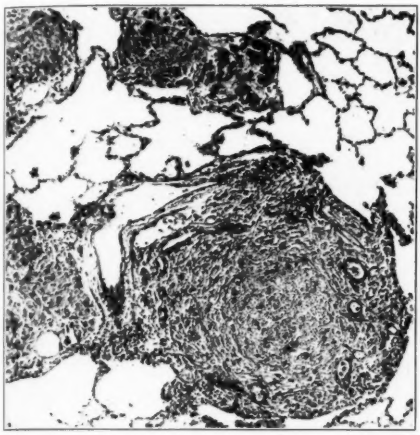
PLATE 3

FIG. 8. Silicotic nodules from the lung of a rabbit exposed to quartz dust for 13 months and allowed to survive 17 months in a normal atmosphere. The large nodule has a necrotic center with a periphery of compressed fibroblasts. The smaller foci are made up of epithelioid cells. × 64.3.

FIG. 9. Silicotic nodule from the lung of a rat inhaling quartz for 13 months and then killed. The center of the lesion is necrotic; its periphery is composed of polygonal mononuclear cells infiltrated with lymphocytes. × 130.

FIG. 10. Silicotic nodule from spleen of rabbit injected intravenously with 0.5 gm. of silica particles less than 3 μ in diameter. Dose administered in 20 injections over a period of 2 months; animal killed 3 weeks later. The center of the nodule is undergoing necrosis although the outlines of the cells are still visible. Fibrous laminas infiltrated with lymphocytes surround the lesion. × 64.3.

FIG. 11. Calcified silicotic nodule in the lung of a rabbit inhaling quartz dust for 6 months and allowed to live 12 more months in a normal atmosphere. The compressed hyaline fibrous laminas about the periphery show but few nuclei. × 64.3.



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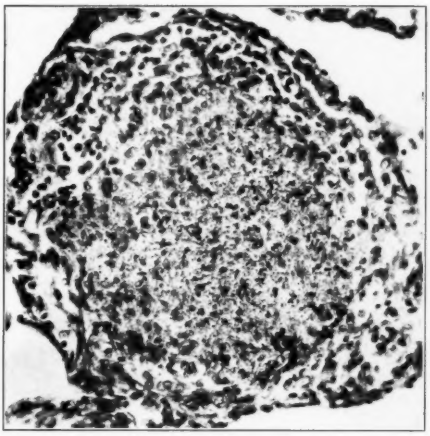

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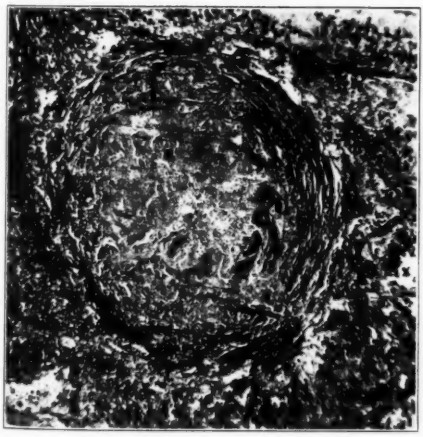

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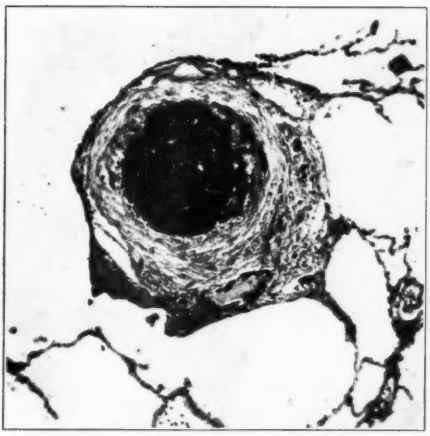

11

Gardner Lesions Produced by Silica and Tubercle Bacillus

STUDIES ON INFLAMMATION *

XIII. Carbohydrate Metabolism, Local Acidosis, and the Cytological Picture in Inflammation

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Earlier studies by one of us [1] have indicated that the cellular picture in an area of inflammation is apparently a function of the local hydrogen ion concentration. The usual cytological sequence in the development of the acute inflammatory reaction consists of an initial infiltration of polymorphonuclear cells that are subsequently replaced by an abundance of macrophages. This change in the cellular elements is correlated by the development of a local acidosis at the site of inflammation. In the initial phase, when the polymorphonuclear cells predominate, the pH of the exudate is definitely within an alkaline range (about 7.3 to 7.4). With the progress of the inflammatory reaction the pH may drop to 6.7 or approximately 6.5. Polymorphonuclear cells for the most part seem unable to survive, without being injured, a pH below 7.0. The predominance of mononuclear phagocytes is conspicuous when the pH of the exudate falls to a level ranging between 7.0 and about 6.8. At greater hydrogen ion concentration, as found in frank pus, all or most types of leukocytes appear to be injured. At times the pH of the exudate remains alkaline throughout the period of acute inflammation. This is invariably attended by a maintenance of the polymorphonuclear phase, indicating thus a probable interrelation between the hydrogen ion concentration and the cellular elements of an exudate. In brief, by determining the hydrogen ion concentration of an inflammatory exudate the character of the cytological picture can be predicted with a fair degree of certainty. Likewise the converse follows. Evidence obtained in a previous study showed that the development of local acidosis in an area of inflammation precedes at times the changes occurring in the differential leukocyte formula of the exu-

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date.[1] In such cases, however, the cytological shift to the macrophage stage ultimately follows the development of the acid reaction.

The purpose of this communication is to present observations on the mechanism of local acidosis in inflammation. The elucidation of this mechanism would probably be of distinct aid to a basic understanding of some of the factors controlling the histological manifestations of a variety of infectious lesions. The observations presently to be described indicate the important rôle of the local carbohydrate metabolism in determining the hydrogen ion concentration of an inflamed area.

Since the classical work of Fletcher and Hopkins [2] on the production of lactic acid in amphibian muscle, numerous publications and reviews have appeared dealing with the chemistry of muscular contraction.[3,4] The Meyerhoff-Hill theory on the rôle of lactic acid in the contractile phase has been recently subjected to severe revision owing to the contributions of Embden and Lawaczeck,[5] Fiske and Subbarow,[6,7] and Eggleton and Eggleton,[8] which led to the discovery of phosphocreatine. These investigators pointed out the important relation of phosphate compounds to the chemical dynamics of muscular contraction. It is well known that other tissues besides muscle manifest glycolytic reactions. Gerard and Meyerhof [9] demonstrated that the frog nerve under anaerobiosis forms lactic acid which on readmission of oxygen disappears.[10] Brain tissue, containing a negligible amount of glycogen, forms lactic acid directly from blood sugar.[11] When maintained outside of the body in a milieu deprived of oxygen most tissues form lactic acid from glucose, *i.e.* through the process of glycolysis. Malignant tissue, normal retina and embryonic tissues display a strikingly high rate of glycolysis. Warburg, Posener and Negelein [12,13] pointed out that of a variety of tissues kept in blood plasma and fully oxygenated, only tumor tissue, and particularly malignant tissue, was capable of producing large amounts of lactic acid. This distinction is not strictly correct. There are normal tissues, such as mammalian erythrocytes, which glycolyze in spite of an adequate oxygen supply. Furthermore, Crabtree [14] demonstrated that hyperplastic lymph nodes and inflammatory granulations caused either by tubercle bacilli or by filterable viruses likewise show pronounced aerobic glycolysis. Scheller [15] found that exudates from suppurative lesions display considerable glycolytic activity when incubated for several hours.

Jervell [16] made a series of extensive investigations on the concentration of lactic acid in blood and urine under various pathological states. He pointed out that the normal "oxygen debt" following muscular activity is always present, even during repose, in patients with decompensated cardiac conditions. This explains their unfitness for physical exertion. In anemia, in pneumonia with partial asphyxia, or in advanced pulmonary tuberculosis, hyperlactacidemia is frequently encountered. From these observations Jervell concluded that an augmentation in lactic acid in the venous blood indicates a deficient oxygen supply to the tissues. The consequent incomplete oxidations lead to an accumulation of lactic acid.

One of us has pointed out in earlier studies that the development of an acute inflammatory lesion involves a walling-off process owing to blockage of normal lymphatic drainage.[17] With the initial increase in capillary permeability and the passage of plasma proteins into tissue spaces, the local circulation becomes seriously impaired as evidenced by the "packing" of cells in the capillary lumen. Thrombosis may induce partial or complete obliteration of the vascular channels at the site of injury. The formation of a fibrinous network in the extracapillary spaces restricts the free diffusion of fluid in the affected area. As the reaction progresses in intensity the area of inflammation becomes "shunted off," as it were, from the rest of the organism. It develops its own pH, its own local circulation, and its own metabolism. Gessler [18] has demonstrated that the oxygen consumption and the metabolic rate are increased in an inflamed area. It is conceivable that the impairment of the local lymphatic and vascular circulation may promote in acutely injured tissues a state of relative anoxemia. With interference in normal oxidative reactions there is a possibility that an anaerobic type of glycolytic activity may result.* Lactic acid accumulates in abundance; and with the depletion of the alkali reserve in the area of injury, local acidosis becomes manifest. Owing either to a direct effect or else through the liberation of enzymes active at an acid pH, polymorphonuclear leukocytes degenerate. If the acidity increases beyond a pH of about 6.5, all types of leukocytes are injured and frank pus results.

* In view of the work of Crabtree referred to above, it is, however, possible that, as in the case of neoplasms, acutely inflamed tissues also may manifest some degree of aerobic glycolysis. This question is being investigated further.

The observations about to be described support further the original concept that in acute inflammation the cytological picture is a function of the hydrogen ion concentration.[1] The pH in turn depends on the rate of glycolytic activity and on the available local alkali reserve.*

Experimental

Dogs were anesthetized by the intraperitoneal administration of an aqueous solution of nembutal (about 33 mg. per kilo weight). Pleural exudation was induced by the injection of 1.5 to 2 cc. of turpentine into the right chest. Subsequently a sample of the exudate was withdrawn daily over a period of several days by means of a Luer syringe containing about 1 cc. of 0.1 per cent heparin in saline. On withdrawing the sample several smears were made on slides. A part of the exudate was immediately transferred into a test tube under paraffin oil for pH determination. The rest of the exudate was centrifugalized under oil and the total CO_2 content of the cell-free material determined by the Van Slyke manometric method.[19] Samples of blood were obtained from the heart and centrifuged under oil. Total CO_2 determinations were likewise made on several samples of blood serum.

* The observations reported here and in a preceding communication have all been made on dogs. They have consistently revealed the fact that the pH seems to condition the cytological picture in inflammation. However, in some unpublished observations on the exudates of rabbits the correlation obtained between the cytological picture and the pH of the exudate was not as consistent as observed in dogs. Similar findings have recently been noted by Lurie (*Arch. Path.*, 1936, **22**, 272–288). It is interesting in this connection that in a review of intracellular digestion Opie (*Physiol. Rev.*, 1922, **2**, 552–584) cites the studies of various investigators who have either failed or found considerable difficulty in demonstrating proteolytic enzymes (readily demonstrable in dogs) in the leukocytes of rabbits.

However, preliminary studies, which are now being conducted in this laboratory and which are to be reported *in extenso* in the near future, indicate that direct studies of the degree of glycolysis (rather than resorting to pH measurements alone) in inflamed tissues of rabbits yield data that correlate quite adequately the cytological picture with the local disturbance in carbohydrate metabolism (see abstract in *Am. J. Path.*, 1936, **12**, 725–726).

In a recent careful study Clark and his co-workers (*Am. J. Anat.*, 1936, **59**, 123–173) point out the advisability of correlating the earlier pH studies of the senior author with living cells rather than resorting to fixed smears in order to rule out the possibility of mistaking modified polymorphonuclears for macrophages when the former cells become degenerated. Some observations were therefore made using the supravital technique on living cells. The results obtained indicated, as in fixed preparations, that the initial type of living cells in inflammatory exudates of dogs is the polymorphonuclear, whereas in the later stages of inflammation, when there is a corresponding rise in the hydrogen ion concentration, the preponderance of viable cells is of the macrophage type.

Measurements of the pH were always performed within a short time after withdrawing the sample of pleural exudate. As described in a previous communication,[1] the bicolor system of standards of Hastings and Sendroy [20] was employed in determining the hydrogen ion concentration.

The differential leukocyte counts were made from smears on slides. The cells were stained by the Wright method. In computing the percentage of polymorphonuclears and macrophages, cells were frequently encountered that were so degenerated as to render their identification difficult. These were not included in the final counts.

In the studies concerned with the intermediate carbohydrate metabolism of exudates as compared with that of blood, the samples

TABLE I

Dog No.	Amount of turpentine injected	Duration of inflammation	Volume per cent of CO_2 content		pH		Cytology of exudate	
			Cell-free exudate	Blood serum	Exudate	Blood	Per cent of polymorphonuclears	Per cent of mononuclear phagocytes
	cc.	*hrs./mins.*						
6–2	2	20:30	40.9	45.4	7.4	7.5	86	14
		43:45	38.6	41.1	7.15	7.5	85	15
		68:15	29.0	45.0	6.5	..	18	82
		91:30	30.4	46.6	6.7	7.5	7	93

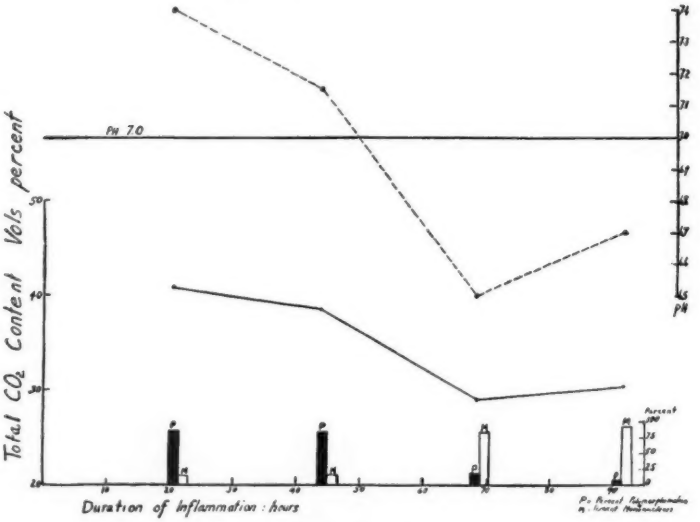
were obtained from the pleural cavity of dogs as described above. Lactic acid determinations were performed on exudates and whole blood by the method of Friedemann and Graeser.[21]* Blood and exudate sugar were determined by the technique of Folin.[23] Measurements of the hydrogen ion concentration and the cytological studies were likewise performed on these samples as described above.

In order to obtain a definite state of local acidosis in the inflamed area the reinjection of the irritant on the 3rd or 4th day was often found to be a convenient means of ensuring a significant fall in the pH.

* Stewart and his collaborators [22] claim that the ordinary methods for determination of lactic acid in muscle appear to yield results that are too high owing to interference by methyl glyoxal. Accordingly they advise removal of this substance by distillation prior to the treatment with copper-lime. Several determinations on exudates and blood after removal of methyl glyoxal yielded practically the same values for lactic acid as when this precautionary measure was omitted. To rule out the possibility that the lactic acid might primarily be derived from glycogen, several determinations for the presence of this substance in exudates were made. Glycogen could not be recovered to any measurable extent.

The Depletion of the Alkali Reserve in Acute Inflammation

With the gradual development of local acidosis in an area of inflammation, the CO_2 content of the cell-free exudate correspondingly tends to fall. Analysis of blood serum, however, reveals no appreciable change in its CO_2 content. The point is illustrated in Table I which summarizes a type experiment.



Text-Fig. 1

The hydrogen ion concentration and the carbon dioxide capacity in relation to the cytological picture of a pleural exudate (Dog 6–2). Note that concomitantly with the fall in pH and alkali reserve there is a shift from a predominance of polymorphonuclear cells to a phase where mononuclear phagocytes constitute the chief element.

-------o------- pH of exudate

———·——— Total CO_2 content (volumes per cent) of cell-free exudate

▮ Percentage of polymorphonuclear cells

▯ Percentage of mononuclear phagocytes

This same data is graphically presented in Text-Fig. 1. The interrelation between pH, CO_2 content, and the cytological picture is quite apparent. With the fall in pH there is a concomitant reduction in the local alkali reserve, as measured by the CO_2 content. Parallel

with these changes in the acid-base equilibrium, the polymorphonuclear cells become displaced by mononuclear phagocytes. If the exudate remains alkaline throughout the period of the acute reaction, the CO_2 content likewise fails to be reduced. On the other hand, if a frankly purulent exudate develops with a pH of 6.5 or below, the CO_2 content may fall to about 8 volume per cent or less. The leukocytes in such types of viscous suppurating material are for the most part swollen, degenerated, and identified, if at all, only with the greatest of difficulty. The depletion in the alkali reserve adequately accounts for the production of an uncompensated acidosis at the site of inflammation.

The Mechanism of Local Acidosis in Inflammation

Studies were undertaken to determine the nature of the acid produced in an area of inflammation. The experiments of Ito [24] had indicated the formation of d-lactic acid by the autolysis pus. Furthermore, as stated in the introductory portion of this paper, it is reasonable to suppose that with the impaired fluid exchange in an area of injury an anaerobic type of glycolytic respiration might prevail. This would manifest itself in a conversion of sugar into lactic acid. If the rate of glycolysis were to increase with no augmentation in the available alkali reserve, an uncompensated acidosis would necessarily result in the inflamed tissue. This seems to be precisely the course of events as indicated by the observations recorded in Table II. Five variable factors were studied in each experiment as follows: time relations, exudate and blood sugar, blood and exudate lactic acid, pH of blood and exudate, and the cytology of the exudate. All these variables in the case of the inflammatory exudate displayed what seemed to be a certain amount of interdependence. Fluctuation of one factor was inevitably followed by corresponding changes in the remaining variables. This is conveniently illustrated in Text-Fig. 2, in the case of Dog 9–2. For the first 3 days the pH of the exudate is alkaline and the polymorphonuclear cells predominate. The lactic acid concentration is relatively low; the level of the exudate sugar either equals or, as a rule, exceeds slightly that of the lactic acid (Table II). On the 3rd day the inflammatory reaction is accentuated by the reintroduction of the irritant. The level of the exudate sugar drops rapidly while the concentration of lactic acid correspondingly increases (Text-Fig. 2).

TABLE II

The Relation of Lactic Acid Level to the Hydrogen Ion Concentration and to the Cytological Picture in Acute Inflammation

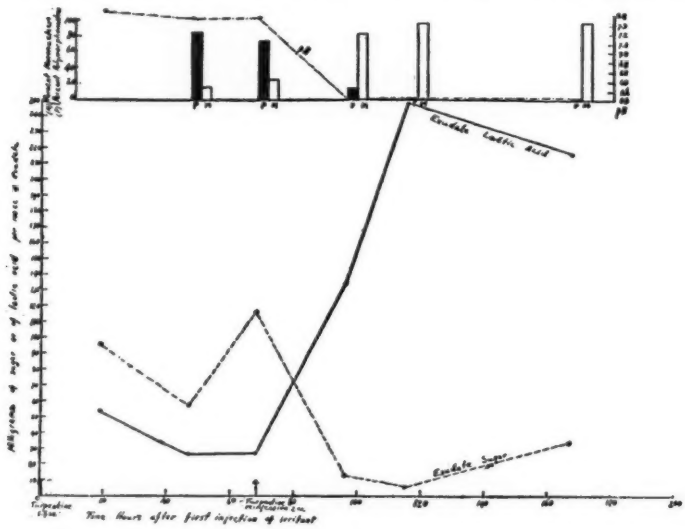
Dog No.	Amount of turpentine injected	Total duration of inflammation	Sugar (mg. per 100 cc.)		Lactic Acid (mg. per 100 cc.)		pH		Cytology of exudate	
	cc.	hrs./mins.	Blood	Exudate	Blood	Exudate	Blood	Exudate	Per cent of polymorphonuclears	Per cent of mononuclear phagocytes
9–2	1.5	0:0	100.0	..	..	..	7.50	..	..	..
		19:10	88.1	96.0	10.8	54.6	7.45	7.43	Relatively acellular	
		47:10	111.9	57.9	13.0	27.0	7.48	7.33	85	15
		68:0	145.5	116.8	16.0	27.8	7.48	7.33	74	26
	2.0 reinjected									(few
		96:15	81.2	13.9	21.9	135.8	7.43	6.5	15	85 cells)
		115:0	138.6	6.4	38.4	248.6	7.43	6.5	2	98
		167:0	138.6	34.7	14.7	217.1	7.45	6.5	2	98
9–1	3.0	0:0	87.1	..	18.1	..	7.55	..	..	..
		19:0	76.2	52.5	14.3	59.9	7.45	7.30	90	10
		47:05	82.2	48.0	..	..	7.43	7.43	66	34
		67:45	102.0	89.1	..	..	7.43	7.28	82	18
	2.0 reinjected									
		95:50	81.2	12.6	10.3	..	7.43	6.5	Relatively acellular	
		114:40	86.1	9.9	11.3	147.8	7.43	6.5	8 (degenerated)	92
8–1*	3.0	0:0	108.9	..	9.2	..	7.33	..	..	..
		20:0	94.1	49.5	13.8	39.6	7.40	7.30	Acellular	
		46:15	141.1	76.8	14.4	48.9	..	7.17	84	16
		68:15	108.9	42.6	27.4	69.7	7.45	7.33	90	10
		95:45	141.6	46.0	24.5	58.0	7.48	7.33	88	12
	1.5 reinjected									
		115:0	81.2	12.9	10.0	110.5	7.48	6.83	Relatively acellular	
		140:0	..	..	..	..	..	6.6	4	96

		140:0	..	..	..	..	..	6.6	4	96
		0:0	78.2	..	9.7	..	7.48	..	..	..
	3.5	20:0	..	..	14.9	94.6	7.48	7.25	Relatively acellular	
		47:45	90.1	18.8	11.5	101.1	7.50	6.93	44	56
		67:45	106.0	38.1	9.2	71.8	7.58	7.10	86	14
8–5*		95:45	118.8	58.2	8.8	55.4	7.50	7.20	84	16
		115:30	92.1	78.2	10.3	57.8	7.45	7.10	67 (degenerated)	33
	1.5 reinjected	142:50	133.7	15.8	7.1	198.1	7.35	6.5	6	94 (degenerated)
		0:0	74.3	..	16.7	..	7.48	..	..	..
	3.0	24:10	64.4	21.8	32.6	88.5	7.38	7.15	Acellular	
7–9*		72:20	95.0	40.6	21.2	91.4	7.40	6.88	28	72
		94:55	114.8	58.9	9.9	78.8	..	7.15	72	28
		0:0	90.1	..	9.2	..	7.33	..	..	..
	3.0	27:20	..	63.4	..	52.1	..	7.18	Acellular	
8–3**		49:35	..	28.7	..	48.1	..	7.30	92	8
		76:55	118.8	58.4	14.7	66.0	7.48	7.05	No count — preponderance of monuclears	
		96:35	121.8	72.8	15.3	37.2	7.48	7.30	70	30
		0:0	92.1	..	8.3	..	7.48	..	..	..
	3.5	19:30	..	..	11.9	57.4	7.35	7.33	Acellular	
		47:20	87.1	13.9	31.2	144.4	7.55	6.75	Preponderance of mononuclears. Shrunken, vacuolated, degenerated leukocytes	
8–4**		67:20	103.0	23.3	11.8	132.0	7.55	6.6	24 (degenerated)	76
		95:30	150.5	15.1	13.4	134.9	7.50	6.70	22 (degenerated)	78
	No injection of acetamide for 3 days. (See footnote)	115:05	117.8	10.1	15.5	128.9	7.50	6.80	12	88
		215:45	93.1	93.1	15.4	52.1	7.60	7.50	Leukocytes are degenerated and vacuolated 76	24

* Dogs Nos. 8–1, 8–5, and 7–9 received, in addition, daily injections of distilled water into the right pleural cavity.

** Dogs Nos. 8–3 and 8–4 received, in addition, daily injections of 1:1000 M mono-iodo-acetamide solution into the right pleural cavity.

The hydrogen ion concentration increases to a pH of 6.5. Polymorphonuclear leukocytes are found wanting or appear in small numbers as degenerated, swollen or distorted cells. The bulk of the cellular element consists of mononuclear phagocytes (*cf.* Text-Fig. 2, Fig. 2). Frequently on the 1st day following the injection of the



TEXT-FIG. 2

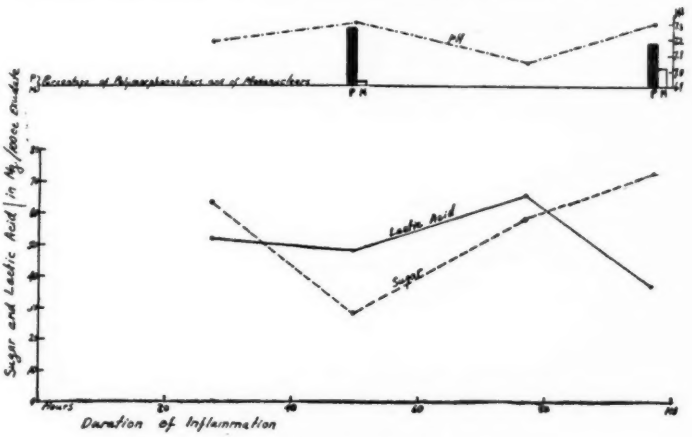
Correlation between the hydrogen ion concentration, the conversion of sugar to lactic acid, and the cytological picture of a pleural exudate (Dog 9–2). Note that with the fall in the level of the exudate sugar there is a rise in the concentration of lactic acid and the pH falls notably. This local acidosis is accompanied by a shift in cellular elements. The polymorphonuclear leukocytes are replaced by mononuclear phagocytes.

—·—·—·— pH
———·——— Lactic acid
———o——— Exudate sugar
▮ Percentage of polymorphonuclear leukocytes
▯ Percentage of mononuclear phagocytes

irritant, the exudate is found to be relatively acellular. Comparison of lactic acid and sugar figures in both blood and exudate reveals an interesting type of reciprocal relations (Table II). The blood sugar level is high compared to that in exudate, while the opposite is true in the case of lactic acid. It is conceivable that this state of affairs

may in part be referable to a higher degree of oxygen saturation in the circulating blood as compared to that in tissues.

The inflammatory reaction is not necessarily conducive to a state of local acidosis. The maintenance of an alkaline pH is, however, invariably associated with a predominance in the exudate of polymorphonuclear cells.[1] In such circumstances the abrupt conversion



TEXT-FIG. 3

Correlation between the hydrogen ion concentration, the exudate sugar, the lactic acid, and the cytological picture of a pleural exudate (Dog 8–3). Note that with the relatively low degree of glycolysis the pH is maintained at an alkaline range and the polymorphonuclear cells predominate throughout the course of the inflammatory reaction.

—·—·—·— pH
———·——— Lactic acid
———o——— Exudate sugar
▮ Percentage of polymorphonuclear leukocytes
▯ Percentage of mononuclear phagocytes

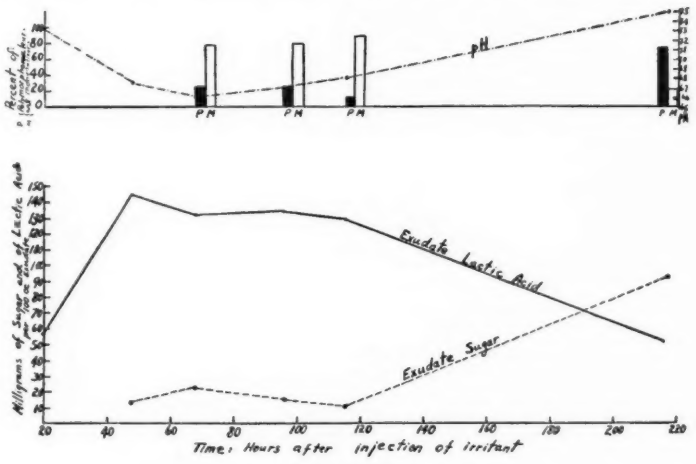
of sugar to lactic acid, as described above, fails to occur. This is well exemplified in Text-Fig. 3 (Dog 8–3, Table II). Within a period of 4 days the level of lactic acid failed to exceed 66 mg. per 100 cc. of exudate, and the pH never fell below 7.0. This would suggest that in an inflamed area when the alkali reserve is depleted it is primarily the rate of formation of lactic acid that determines the ultimate degree of acidity.

The studies of Lundsgaard [25] indicated that a muscle poisoned with iodoacetic acid fails to produce lactic acid during the contractile phase. The introduction of iodoacetic acid into the inflamed pleural cavity of dogs was found to be impracticable owing apparently to the toxic action of the drug. Therefore we substituted a daily injection of 10 cc. of a 0.001 M solution of mono-iodo-acetamide into the chest cavity that had previously been inoculated with turpentine.* It was believed that such a procedure might inhibit the glycolytic process and consequently maintain a predominance of polymorphonuclear leukocytes in the inflamed area. The control animals received repeated superimposed injections of distilled water instead of the iodo-acetamide solution (*cf.* Dogs 8–5, 7–9, 8–3, 8–1, and 8–4, Table II). It is clear from the data that iodo-acetamide failed *in vivo* to prevent the usual course of the inflammatory reaction leading to an increase in lactic acid. It is to be noted that in a previous communication one of us had attempted to alter *in vivo* the pH of the area of inflammation by the repeated introduction of phosphate buffers.[1] The effort ended in failure; this served as an additional example of the fact that *in vitro* reactions are not easily reproduced in the living organism. Evidently more information on the mechanism of tissue buffers would be desirable before attempting to modify experimentally the acid-base equilibrium in the extracapillary spaces. In the case of one dog (No. 8–4), the repeated injections of the acetamide apparently even hastened the development of local acidosis (*cf.* Table II and Text-Fig. 4). The lactic acid rose rapidly at the expense of the sugar level and the pH correspondingly fell. There was a preponderance of mononuclear phagocytes. After about 1 week the daily injections of iodo-acetamide were discontinued for a period of 3 days. At that time the pH was found to be alkaline, the exudate sugar had risen with a corresponding drop in lactic acid, and the cellular content consisted now primarily of polymorphonuclear leukocytes (Text-Fig. 4). The observations on this particular dog suggest that with cessation of daily injections of mono-iodo-acetamide reparative processes of vascular organization were favored; thus the sprouting of new capillaries permitted wider opportunity for oxygenating the inflamed tissue. This state of affairs probably tended to decrease the glycolytic rate and thereby the hydrogen ion concentration.

* This substance was obtained through the courtesy of Dr. G. Pincus.

Discussion

The foregoing observations, in addition to evidence obtained in a previous communication,[1] indicate that the cytological picture in an area of acute inflammation is apparently conditioned by the local pH, which in turn is determined by the rate of lactic acid formation



Text-Fig. 4

The hydrogen ion concentration, the lactic acid, the exudate sugar, and the cytological picture of a pleural exudate (Dog 8–4). This animal received in addition daily injections of a solution of 0.001 M mono-iodo-acetamide into the affected pleural cavity for about a week. Note the failure in inhibiting the sharp initial glycolysis with the concomitant rise in the hydrogen ion concentration. The mononuclear phagocytes form the predominating cellular element. On discontinuing the injections of iodo-acetamide the pH rose and the glycolytic activity was found to be considerably diminished. At this stage the polymorphonuclear cells assumed the ascendancy.

—·—·—·— pH
———·——— Lactic acid
----o---- Exudate sugar
▮ Percentage of polymorphonuclear leukocytes
▯ Percentage of mononuclear phagocytes

and the depletion of the alkali reserve at the site of injury. With progress in the intensity of the inflammatory reaction there is a tendency for increased glycolytic activity as revealed by a rise in lactic acid formation. This is accompanied by a fall in the carbon

dioxide capacity and the pH correspondingly drops. A true lactic acid acidosis results at the site of inflammation. The polymorphonuclear leukocytes apparently survive only when the pH is alkaline (Text-Fig. 1, Fig. 1). As the pH falls below 6.7 or thereabouts, all types of leukocytes tend to be injured and frank pus develops. It is conceivable that the mechanism of suppuration is in part referable to the development of this local acidosis resulting from an increased glycolysis. The high degree of acidity may well act as a toxic factor on leukocytes. The studies of Evans [26] indicate that these cells are sensitive to the action of acids. It is also possible that the development of an acid pH favors the action of proteolytic enzymes released from leukocytes (*e.g.* pepsin and cathepsin) as well as that of other tissue autolytic enzymes.[27,28] Studies on the mechanism of suppuration are now in progress and will form the subject of a separate future communication.

The present observations indicate the important rôle of disturbed carbohydrate metabolism in an area of injury. In view of the available evidence, it is likely that differences in histological manifestations of various infectious lesions may be referable to disturbances in the intermediary carbohydrate metabolism of the affected tissue. It is conceivable that the intensity and severity of an inflammatory reaction is primarily referable to its capacity for bringing about the incomplete oxidation of carbohydrates. In this connection it is interesting to note that within a given interval of time *Staphylococcus aureus* induces a lesion characterized by a greater glycolytic activity than does *Streptococcus hemolyticus*. Previous work had demonstrated that the localization of staphylococci in contrast to the invasiveness of hemolytic streptococci was primarily referable to the greater necrotizing capacity of the former microorganism.[29,30] The implications of such a concept in regard to possibly providing an adequate explanation for the well known fulminating character of infectious lesions in the diabetic condition are sufficiently obvious without warranting any additional comment.

Several problems of theoretical interest arise as a result of the present series of experiments, suggesting some similarity between the chemical dynamics involved in muscular contraction and in the development of the inflammatory reaction. For instance, it is well known that hexosephosphate represents an intermediary product in the breakdown of glycogen to lactic acid. Cori and Cori [31] have

demonstrated that tetanic stimulation of muscle yields hexosephosphate. Under anaerobic conditions the removal of this compound is affected by glycolysis for it is accompanied by an equivalent increase in lactic acid and by the liberation of inorganic phosphate. The writers have accordingly studied the inorganic phosphate content of cell-free exudates and compared it with that in samples of blood serum. In the initial stages of inflammation the level of phosphates in exudates is slightly higher than in serum. After several days, however, when the inflammatory reaction has progressed in intensity and the exudate assumes a purulent character, the phosphate content is found to be several times more elevated in the cell-free exudate than in the serum. Concomitantly, as pointed out in this communication, the lactic acid concentration is found to be considerably augmented. This would strongly suggest a similarity between the changes in carbohydrate metabolism during muscular activity and those occurring in an acutely inflamed area where there presumably develops a state of relative anoxemia owing to impaired local vascular and lymphatic circulation.[17]

Rubel [32] has recently studied the relation between glycolysis and proteolysis in tissues. The observations of this investigator indicate that an increase in glycolytic activity of tissue is accompanied by an accumulation of amino and of non-protein nitrogen, whereas inhibition of glycolytic activity is followed by a diminution of proteolytic processes. It may be noted here that parallel determinations in exudate and blood serum have invariably revealed a higher concentration of amino acid nitrogen in the exudate than in the blood serum.[33] This difference in level was particularly striking in the later stages of the inflammatory reaction at a time when the lactic acid concentration was elevated. Furthermore, the concentration of total protein nitrogen was found to be lower in the exudate than in the corresponding samples of blood serum. This reciprocal relation between amino acids and total protein nitrogen in exudate and serum suggests active proteolytic processes at the site of inflammation, particularly at the time when the rate of glycolysis is considerably enhanced.

Hegnauer, Fenn and Cobb [34] have recently pointed out that in muscles of frogs with notable increase in potassium concentration, irritability is completely held in abeyance and simultaneously lactic acid production begins to be enhanced. In a recent study from this

laboratory [35] it has been shown that in an inflammatory exudate the concentration of potassium is about twice as high as in serum, even in the earliest phase of the reaction. Whether this high concentration of potassium in inflammation is in any way related to the increased glycolytic rate remains to be determined.

In brief, various questions on the chemistry of inflammation suggested by the present line of investigation are being studied further in an endeavor to obtain a clear notion of the relation of the intermediary products of carbohydrate metabolism to differences in the morphological manifestation of a variety of infectious lesions. These studies will form the subject of separate reports in the future.

Summary and Conclusions

With the development of an acute inflammatory reaction the carbon dioxide capacity of the cell-free exudate progressively diminishes. This is correlated with an increase in the hydrogen ion concentration and by a concomitant shift in the cellular composition from a polymorphonuclear to a mononuclear phagocytic phase. When the pH drops below 6.7 or 6.5, most of the leukocytes appear to be injured and frank suppuration ensues.

An inflammatory exudate manifests greater glycolytic activity than blood, as indicated by the higher level of exudate lactic acid and a correspondingly lower concentration of exudate sugar.

The rate of glycolysis increases as the inflammatory reaction progresses in intensity. Within several days, particularly if the reaction has been intensified by reinoculating the irritant, the concentration of lactic acid is considerably augmented and the result is a localized lactic acid acidosis.

The evidences indicate that the mechanism of local acidosis in inflammation is therefore primarily referable to an increase in the rate of glycolysis and a consequent depletion of the alkali reserve. With the increase in the hydrogen ion concentration to a pH below 7.0 polymorphonuclear leukocytes seem unable to survive and the predominating infiltrating cell is the mononuclear phagocyte. A maintenance of an alkaline pH resulting from relatively diminished glycolytic activity is accompanied by a preponderance of polymorphonuclear leukocytes with no subsequent shift in the cellular constituents of the exudate.

The available evidence indicates that the cytological picture in an

area of acute inflammation appears to be conditioned by the local pH which in turn depends on the rate of glycolysis and the depletion of alkali reserve. The significance and implications of local disturbances in carbohydrate metabolism in determining the severity of an acutely inflamed area have been discussed.

NOTE: We wish to express our appreciation to Miss Hester Blatt of the Children's Hospital for performing the CO_2 determinations, and to Mr. M. Kadish for valuable assistance during the course of this investigation.

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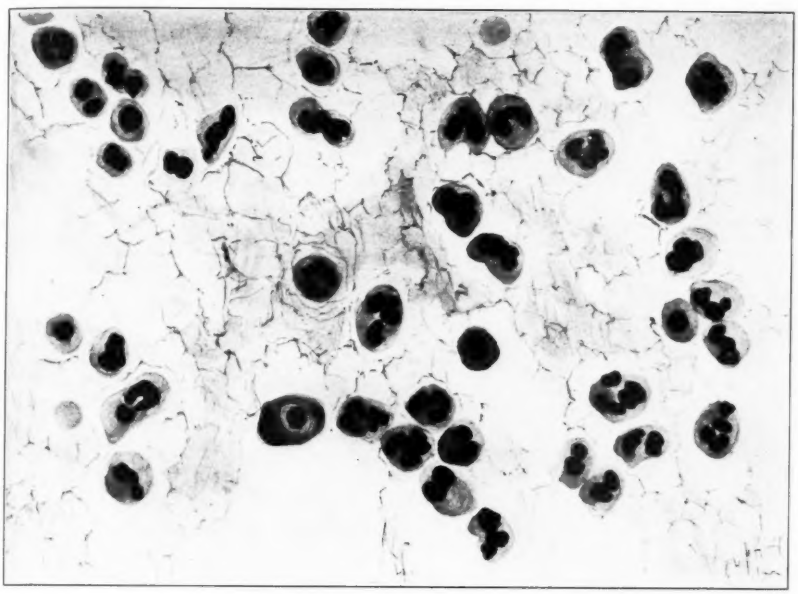
DESCRIPTION OF PLATE

PLATE 4

FIG. 1. Camera lucida drawing of inflammatory reaction induced by the injection of turpentine in Dog 5–0. Reaction is of 24 hours duration. Note preponderance of polymorphonuclear cells; pH of exudate is 7.45. × 1300.

FIG. 2. Camera lucida drawing of inflammatory reaction induced by the intrapleural injection of turpentine in Dog 9–2; reaction is of 1 weeks duration. Note preponderance of mononuclear phagocytes; pH of exudate is approximately 6.5. × 1300.



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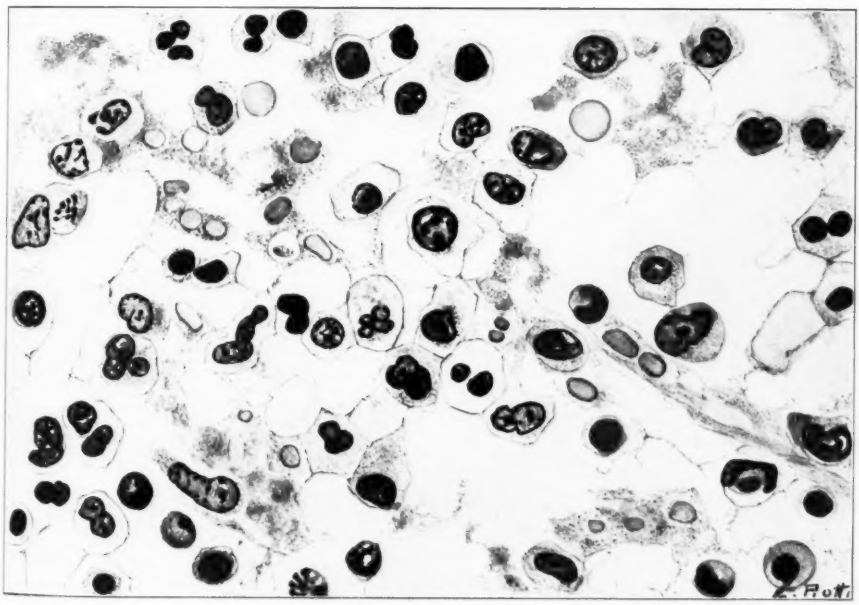

2

HISTOLOGICAL OBSERVATIONS ON TRANSPLANTABLE RAT AND RABBIT TUMORS CULTIVATED IN THE CHORIO-ALLANTOIC MEMBRANE OF CHICK EMBRYOS, WITH SPECIAL REFERENCE TO THE WALKER RAT TUMOR 256*

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The first investigator to cultivate transplantable mammalian tumors in the membranes of chick embryos was Murphy,[1] using mouse and rat tumors. Stevenson [2] cultivated 3 mouse tumors, 2 rat tumors and 1 guinea pig tumor in chick membranes. The recent work [3] on the use of the chorio-allantoic membrane of the chick for the growth of viruses suggested a renewed study of the growth of tumors in this medium. This paper presents a comparative histological study of tumors grown in their native host and in the chorio-allantoic membrane. The tumors studied were the Walker rat tumor 256, the R 39 rat sarcoma and the Brown-Pearce rabbit carcinoma.†

Walker Tumor 256 in the Rat

The Walker tumor has been transplanted in rats in this laboratory since February, 1933. No change in the histological characteristics has been observed during this time.

The tumor grows expansively in the subcutaneous tissues of the rat. It appears at autopsy as a firm, spherical, encapsulated nodule which does not infiltrate the overlying skin or underlying muscle. The cortex of the cut tumor is pink, smooth and firm, and extends for varying distances into the medulla. The medulla is soft and necrotic with small hemorrhagic areas. Occasionally it contains one or more cysts filled with cloudy or bloody fluid. The central necrotic area is not present in very small tumors.

Microscopic examination of the Walker tumor (Fig. 1) shows that it is composed of large, elongated and spindle shaped cells extending in different directions and sometimes occurring in bundles. The nuclei of these cells are large, and oval or elongated. Each nucleus

* Aided by a grant from the International Cancer Research Foundation.

† Dr. Francis C. Wood kindly supplied the R 39 sarcoma, and Dr. Albert E. Casey the Brown-Pearce carcinoma.

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contains fine chromatin granules and a large nucleolus. Many of the cells are in mitotic division. The stroma is quite profuse and consists of collagenous fibers separating the cells. The tumor has the appearance of a fibrosarcoma.

Walker Tumor 256 in the Chick Membrane

Tumor cell suspensions were prepared by the methods described in a previous paper.[4] The eggs were prepared by the shell-flap method described by Goodpasture and Buddingh.[3] The suspensions were dropped in 0.1 to 0.01 cc. amounts on the chorio-allantoic membranes of 8-to-10-day incubated eggs.

Spherical nodules, usually 4 mm. in diameter, developed on the membranes in 7 days. These nodules are composed of large polygonal cells with large round nuclei (Fig. 2). Many of the cells are in mitotic division. The stroma consists of a small amount of fibrous tissue surrounding groups of malignant cells. Many blood vessels filled with chicken blood cells can be seen among the tumor cells. The nodules are not encapsulated. Numerous isolated tumor cells infiltrate the connective tissue of the membrane. The infiltrating cells are usually round or oval. Some of these cells are in mitotic division. The tumor does not infiltrate the endoderm or ectoderm but is separated from these cells by a layer of fibroblasts. A few tumors have small alveolar spaces surrounded by malignant cells (Fig. 3). The histological appearance of the Walker tumor cultivated in the chick membranes in eight separate experiments is that of a carcinoma.

The histological characteristics of the Walker tumors obtained from the rat and from the chorio-allantoic membrane are different in several respects. The tumor from the rat is encapsulated and is characterized by spindle cells separated by collagenous fibers. The tumor from the chick membrane has no capsule and is composed of infiltrating polygonal cells. The Walker tumor in the rat has the appearance of a sarcoma, the tumor in the chick membrane that of a carcinoma.

R 39 Rat Sarcoma

This tumor in the rat is a typical encapsulated fibrosarcoma (Fig. 4) with interlacing bundles of compact, large spindle cells separated by a small amount of collagenous fibers. The tumor obtained

from the chick membrane (Fig. 5) is also encapsulated and consists of large spindle cells. Many mitotic figures can be seen. The R 39 tumor, unlike the Walker tumor in the chick membrane, has a definite capsule and there is no infiltration of the connective tissue. No differences can be observed in the histological appearance of R 39 sarcoma cultivated in the rat and in the chick membrane.

Brown-Pearce Rabbit Carcinoma

The Brown-Pearce tumor growing in the testicle of the rabbit (Fig. 6) is encapsulated. Sections of the tumor show strands and whorls of malignant cells. The whorls consist of radially arranged cells surrounding clear spaces. The malignant cell is large, polygonal or columnar, and contains a large, round, lightly staining nucleus with a dark nucleolus and a few chromatin granules. Connective tissue and necrotic débris separate the strands and whorls.

The tumor growing in the chick membrane (Fig. 7) is composed of the same type of malignant cell as observed in the testicular tumors. The cells are compact and stimulate the production of very little stroma. Many cells show mitotic figures. The tumor nodule is not surrounded by a capsule. A few malignant cells invade the mesoderm. The chick membrane tumor does not have the whorls seen in the testicular tumors. Both tumors, however, are typical carcinomas.

Discussion

Transplantable tumors cultivated in the chorio-allantoic membranes of chick embryos have the same histological structure as the tumors growing in their native host. This similarity in structure is brought out by Murphy's work on the Jensen rat sarcoma, by Stevenson's observations on 6 tumors of the mouse, rat and guinea pig, and by the work reported here on R 39 sarcoma and the Brown-Pearce carcinoma.

The Walker tumor 256 is, however, an exception. The tumor in the rat appears to be a sarcoma, while that in the chick membrane appears to be a carcinoma.

The history of the tumor, interestingly enough, indicates that it is not a true sarcoma. The tumor originated as a spontaneous mammary adenocarcinoma. It lost its adenomatous structure on transplantation. Further transplantations caused further changes so that some pathologists diagnosed the tumor as a carcinosarcoma.[5]

The tumor cultivated in this laboratory has the histological appearance of a sarcoma. Apparently the histological appearance of the tumor changed from a carcinoma to a sarcoma during the repeated transplantations.

The transformation of the Walker tumor from a carcinoma to a sarcomatoid tumor was actually observed by Earle [6] under controlled conditions. This investigator was working with the carcinomatous form. However, a few of his tumors developing from tissue cultures of the carcinoma "showed a strikingly different form of architecture, simulating fibrosarcoma." Descendants of these transformed tumors maintained the sarcomatoid structure.

The transplantation of the sarcomatoid Walker tumor to the chick membrane stimulated the tumor to revert to the carcinomatoid type of growth. Stevenson [2] also observed that a tumor cultivated in chick membranes has the power to recover antecedent characteristics. He describes a hemorrhagic carcinoma which produced hemorrhagic cysts when cultivated in the chick membrane, but seldom produced these cysts when implanted in mice. The recovery of antecedent characteristics observed in these instances may be ascribed to a more complete differentiation of the tumor cells when cultivated in chick membranes.

To understand the nature of the peculiar transformation of the Walker tumor it is necessary to consider the experiences of other investigators who observed histological changes in other tumors.

The transformation of mouse and rat carcinomas into "sarcomas" is not an uncommon occurrence. The investigators who have observed this change are (according to Woglom [7, 8] and Russell[9]) Ehrlich and Apolant, Loeb, Liepmann, Bashford, Murray and Haaland, Lewin, Stahr and Clunet. Most of these investigators report the sudden appearance of spindle cells in the course of a routine transplantation of a pure carcinoma with the production of a mixed tumor. The spindle cells had a strong tendency to overgrow the carcinoma cells and as a result pure strains of "sarcoma" were obtained after a few transplantations. The sarcomas could be transplanted indefinitely and there was no tendency for the tumor to revert to the original carcinomatous structure. The sarcomas grew more rapidly than the corresponding carcinomas and had a higher percentage of takes, a greater tendency to metastasize, and a higher percentage of regressions.[9]

Human carcinomas have also been reported to give rise to spindle cell tumors. Russell [9] cited 3 cases of transformation: an adenoma of the thyroid which recurred as a carcinoma after one operation, and as a sarcoma after a second operation; a carcinoma of the prostate which was associated with carcinomatous metastases to the bones and a sarcomatous metastasis to the lungs; and a carcinoma of the orbit which recurred after operation as a mixed carcinoma and sarcoma. Ewing [10] traced "an adamantinoma recurring after four operations, through the structures of adult acanthoma, plexiform epithelioma without squamous cells, spindle cell sarcoma, and finally round cell sarcoma." Ewing also found a spindle cell perivascular sarcoma in a uterus shortly after curettage revealing typical adenoma. Wail [11] observed that a metastasis from a carcinoma of the lip to the submaxillary lymph nodes was composed of spindle cells. Wagner [12] reported an epithelioma which recurred after radium treatment as a sarcoma. Martin and Stewart [13] found that treatment of a squamous cell carcinoma by cautery and radium resulted in a spindle cell carcinoma. All these investigators showed that "sarcomas" or spindle cell tumors may develop after the operative removal, irradiation or metastasis of carcinomas.

A number of explanations have been offered to account for the changes in the histological appearances of animal and human carcinomas. Some pathologists consider the transformed tumors to be true sarcomas. Schlagenhaufer and von Hansemann (cited by Russell [9]) believed the sarcomas developed from latent sarcoma cells in the original tumors. Ehrlich and Apolant, and Haaland (cited by Woglom [7]), Woglom,[8] and Russell [9] thought that the sarcomas resulted from the malignant transformation of the stroma of the host. Other pathologists (Ewing[10] and Martin and Stewart [13]) believe that the spindle cell tumors are not sarcomas but that the spindle cells are altered carcinoma cells.

A possible explanation of the transformation of a carcinoma into a spindle cell tumor is suggested by the behavior of benign tumors. It is well known that a benign tumor may, as a result of operative trauma, irradiation or transplantation (Heiman [14]), be transformed into a malignant tumor having an increased growth rate and a tendency to metastasize. It is reasonable to suppose that a malignant tumor may as a result of the same procedures — operative trauma, irradiation and transplantation — be transformed into a

more malignant tumor. The transformation of an adenocarcinoma into a spindle cell tumor may be considered, then, a manifestation of an increase in the malignancy of the tumor cell, and is associated with an increase in growth rate and with a greater tendency to metastasize. According to this hypothesis, Ewing's case of an adamantinoma transforming itself successively into an acanthoma, epithelioma, spindle cell sarcoma, and finally round cell sarcoma, may be interpreted as a step by step increase in the malignancy of the epithelial cells from a benign stage to an exceedingly malignant stage. Earle may have observed an increase in the malignancy of the Walker tumor cells during prolonged *in vitro* cultivation. Perhaps a study of the change of a benign or a malignant cell into a more malignant cell may throw some light on the transformation of a normal cell into a malignant cell.

Summary and Conclusions

The chorio-allantoic membrane of the chick embryo was found to be a suitable medium for the growth of the Walker rat tumor 256, the R 39 rat sarcoma and the Brown-Pearce rabbit carcinoma. The R 39 sarcoma and the Brown-Pearce carcinoma obtained from chick membranes were similar microscopically to the parent tumors obtained from the rat and rabbit. In contrast, all the Walker tumors obtained from the chick membranes differed notably in histological structure from the parent spindle cell tumors obtained from the rat. This change in structure was interpreted as a partial reversion of the Walker tumor to its original carcinomatous structure.

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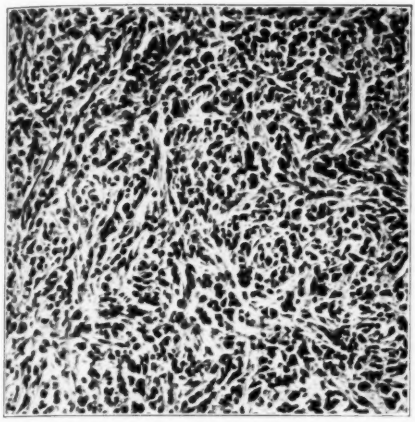
DESCRIPTION OF PLATES

PLATE 5

FIG. 1. Walker rat tumor 256 obtained from a rat. (*a*) × 140 and (*b*) × 600.

FIG. 2. Walker rat tumor 256 obtained from a chick membrane. (*a*) × 140, (*b*) × 600, and (*c*) × 750.

FIG. 3. Walker rat tumor 256 obtained from a chick membrane. × 140.



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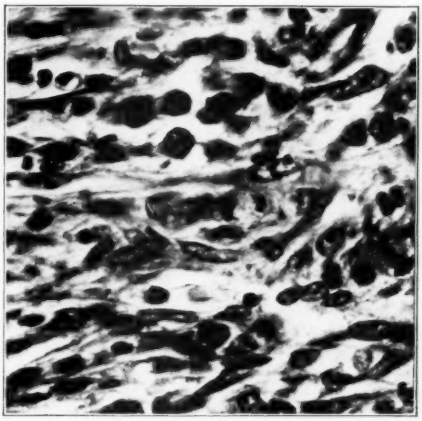

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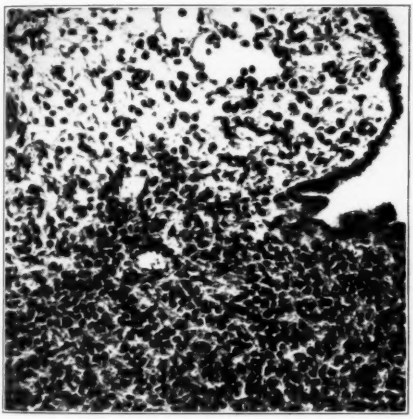

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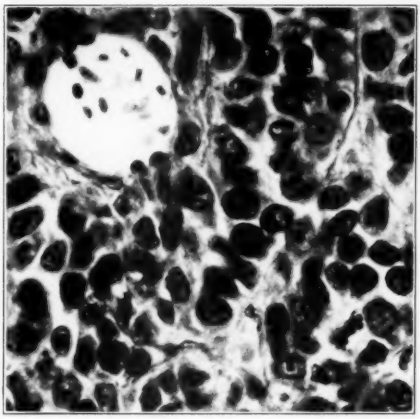

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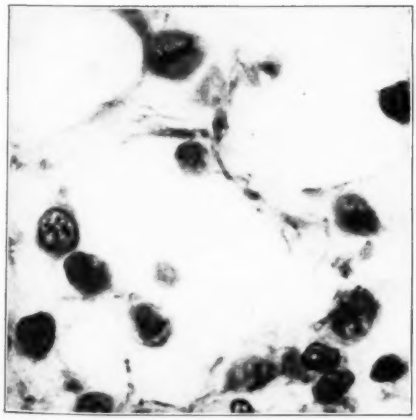

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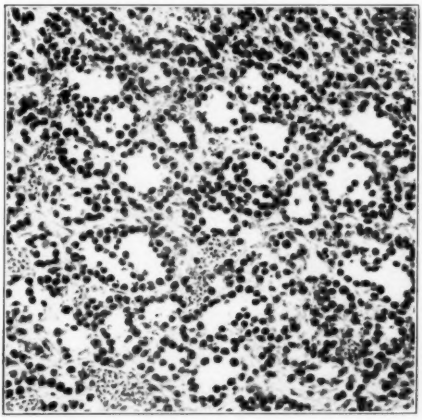

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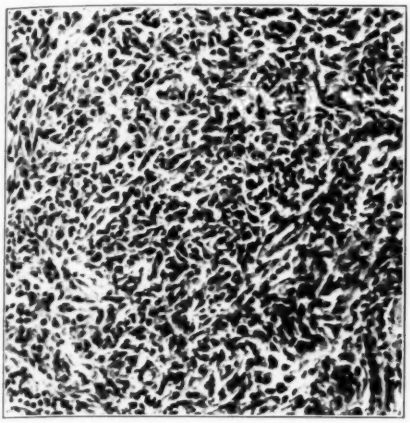
PLATE 6

FIG. 4. R 39 rat sarcoma obtained from a rat. (*a*) × 140 and (*b*) × 600.

FIG. 5. R 39 rat sarcoma obtained from a chick membrane. (*a*) × 140 and (*b*) × 600.

FIG. 6. Brown-Pearce rabbit carcinoma obtained from the testicle of a rabbit. × 140.

FIG. 7. Brown-Pearce rabbit carcinoma obtained from a chick membrane. × 140.



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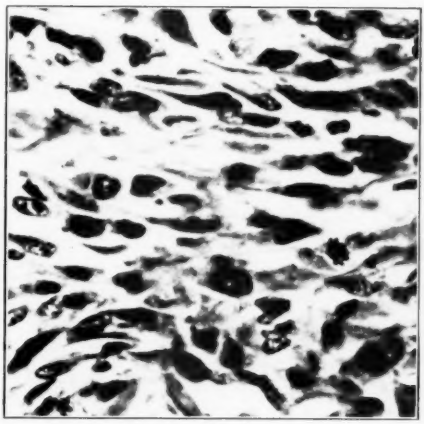

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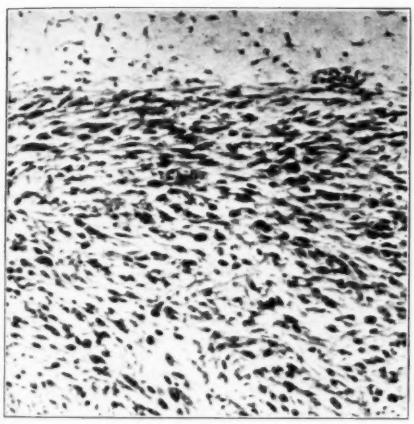

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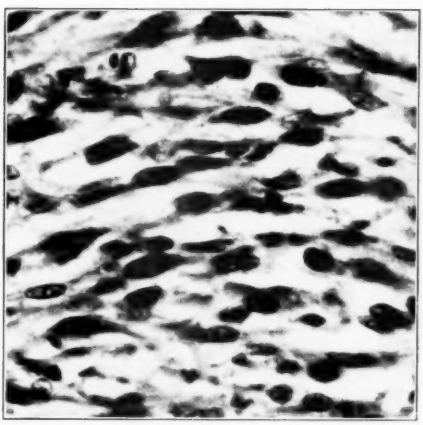

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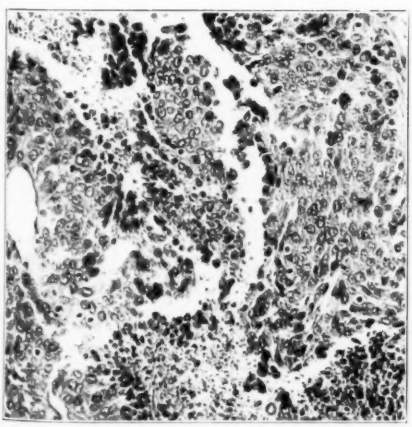

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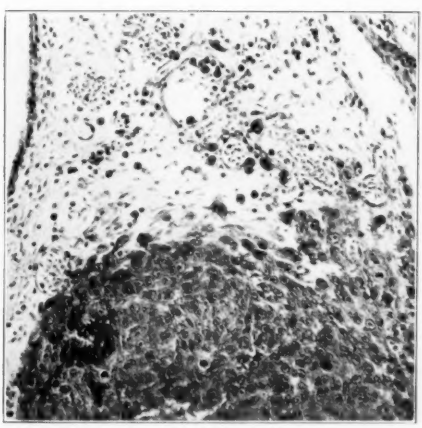

7

MALIGNANT TUMORS OF THE SMALL INTESTINE *

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Introduction

Tumors primary in the small intestine are summarily dealt with in textbooks, seldom diagnosed before operation and, in general, are viewed as clinical rarities. However, a review of the literature reveals that they are not so infrequent as commonly supposed. It is the purpose of this paper briefly to summarize the literature on this subject, and to present 10 primary tumors of the small intestine found at autopsy in this laboratory during the past 40 years.

These tumors have been classified either as benign or as malignant. The benign group includes adenoma, lymphangioma, lipoma, fibroma, myoma and argentaffin tumors, which occur in the relative order of frequency given. Hemangiomas, pancreatic rests and endotheliomas rarely may be found. The malignant group comprises the carcinomas, sarcomas and, rarely, argentaffin tumors.

The literature on sarcoma of the small intestine is extremely confusing and seems confined to occasional reports of single cases of tumor, chiefly of the small round or spindle cell type. However, Nothnagel,[1] in 1904, in a series of 21,358 autopsies reported 243 cases of "intestinal sarcoma" of which 9 occurred in the ileum. In 1905 Corner and Fairbank [2] found a much higher incidence in the small intestine. They stated that of 103 cases of "sarcoma," which they reported, 63 per cent occurred in the small intestine, with the ileum the most common site. Rolleston,[3] in 1901, in 18,000 autopsies at Guy's Hospital found 6 cases of "sarcoma" of the duodenum.

In an excellent review of the subject, Ullman and Abeshouse [4] in 1932 collected from the literature 249 cases of "sarcoma" to which were added 126 cases of their own. They found the small intestine was involved more frequently than the large by a ratio of 2:1. Lymphosarcoma was the predominating type of tumor found and they assumed that many growths previously reported as small or large round cell sarcoma were lymphosarcoma of the lymphocytic or reticulum cell type. The most common site was the ileum, with the jejunum next in frequency. Graves,[5] Crowther,[6] and Rankin [7] had

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previously reported the high incidence of lymphosarcoma of the small intestine. They also concluded that because of errors in diagnosis and variations in nomenclature the majority of tumors previously reported as "primary sarcoma" were in reality lymphosarcoma.

Much may be said concerning the literature on carcinoma primary in the small intestine. Statistics show that carcinoma involving some part of the body is found in 10 per cent of all autopsies. According to Ewing,[8] 8.56 per cent are primary in the gastro-intestinal tract, exclusive of the stomach. Ninety-three per cent of these occur in the colon and rectum, 3 per cent in the jejuno-ileum, and 4 per cent in the duodenum. Rolleston [3] stated that primary carcinoma of the small intestine is "decidedly rare" and reported only 4 cases in 18,000 autopsies. Schlesinger [9] found 17 cases in 42,000 autopsies at the Vienna General Hospital, where out of 3585 cases of carcinoma 343 were primary in the intestines. Judd [10] in 1919 reported that in a number of clinics 3 per cent of intestinal carcinomas were primary in the small intestine. He quoted the incidence of cases primary in this site at the Mayo Clinic as being 0.062 per cent of all cases of carcinoma from the stomach to the rectum. Rankin and Mayo [11] in 1925, including Judd's, found 55 cases at the same clinic. During this period there had been 4597 carcinomas of the large intestine and 4335 of the stomach. In Brill's [12] collected statistics only 2.5 per cent of intestinal carcinomas were primary in the small intestine, with the duodenum and ileum being involved with equal frequency. Hinz [13] found 18 cases in 584 cases of intestinal carcinoma. Bunting [14] reported but 1 case in 2200, and McKenty [15] found only 2 cases in 2500.

The site of predilection for carcinoma of the small intestine seems to vary with the author, but Rolleston,[3] Bland-Sutton,[16] Jefferson,[17] Deaver and Ravdin,[18] and Eusterman, Berkman and Swan,[19] all agree that the duodenum is the most common location. In reviewing statistics Meyer and Rosenberg [20] in 1931 found that primary carcinoma of the duodenum occurred in 0.01 to 0.1 per cent of all autopsies, with the most common figure 0.01 to 0.03 per cent. Of carcinoma of all parts of the body, 0.04 to 1 per cent were primary in the duodenum, with the most common figure 0.2 to 0.4 per cent.

In other series of cases the jejunum has more frequently been the primary site. From 1915 to 1919, Lahey,[21] Jefferson,[17] and Judd [10]

reported 24 cases of carcinoma of the small intestine, of which 11 occurred in the jejunum. Rankin and Mayo [11] found that 21 of their 55 cases originated here.

It would seem, therefore, that carcinoma primary in the small intestines is not so rare as commonly believed, and that when it occurs it is most frequent in the proximal portion.

In further analysis of carcinoma of the duodenum Pic [22] first divided the cases into three anatomical types: (1) parapyloric, (2) peri-ampullary, and (3) prejejunal. This classification has been quite rigidly adhered to and figures show a marked predominance of the peri-ampullary location, with the least incidence in the prejejunal position. However, considerable care must be used to exclude cases primary in the ampulla or in the distal portion of the common duct.

Etiology

Many theories have been offered to explain the etiology of primary tumors of the small intestine. Geiser [23] suggests two theories: (1) that the condition is due to irritation, with a fold of mucosa becoming chronically irritated by duodenal contents; and (2) that in the area about the ampulla there are two types of epithelium in contiguity, with resultant proclivity to malignant degeneration. Rankin and Mayo [11] postulate the fluid nature and alkalinity of the contents and the absence of abrupt bends as explanation of the relative rarity of neoplasms of the small intestine. In the colon, stasis and the different nature of the contents may play a part in the greater incidence of carcinoma. Malignant degeneration of chronic ulcers has occasionally been offered as the cause. However, although one would expect a greater incidence of carcinoma where ulcer commonly occurs, the reverse is true. Jefferson [17] in 1916 collected 19 such cases and added 1 of his own, but even he was not entirely convinced of this theory and concluded that "some are doubtful." Orth claims that they may arise from morbid changes in Brunner's glands, and Cohnheim states that they originate from aberrant pancreatic tissue (quoted by Meyer and Rosenberg [20]). McGuire and Cornish [24] believe that aberrant gastric tissue is the exciting agent, but according to Bland-Sutton [16] there is insufficient evidence to warrant these views and the theories of pancreatic rests and changes in Brunner's glands "belong to the domain of fiction." Gallstones have been

thought to be a cause by virtue of irritation, but they are more common in females in whom carcinoma is less frequent. Syphilis occurs in a few cases but is probably not significant.

Anatomical relations have been discussed by Forgue and Chauvin [25] to explain the greater incidence in the duodenum. They hold that fixation by the parietal peritoneum, the four flexures, and the fact that the duodenum is the most widely dilated portion, which predisposes to stasis, are important factors.

Material

This report is based on a study of 10 cases of primary neoplasm of the small intestine occurring in 11,206 autopsies performed in this laboratory over a period of 40 years (1896–1935). During this time 5 surgical cases also were observed, but as this paper is a study of anatomical location, incidence and site of metastases, they are not included. Primary tumors of the ampulla and common duct were excluded also and no autopsied cases of tumors of lymphoid tissue were found.

Of these cases, 2 were sarcoma and the remaining 8 carcinoma. In this same period 343 cases of carcinoma of the gastro-intestinal tract from esophagus to rectum were found. This gives an incidence of 2.33 per cent of carcinoma of the small intestine in relation to carcinoma of the intestinal canal.

Summary of Pathological Findings

Table I gives the essential details of the 10 cases. From this it will be noted that 8 of the cases were primary in the duodenum, with the remaining 2 arising in the jejunum.

As is true of malignant disease elsewhere, neoplasms of the small intestine are a disease of the middle or late middle-age group. The average age in the series reported in the literature varies from 47.5 to 59 years, with the usual figure about 53 years. In this present series the average age was 57 years, with the youngest 30 and the oldest 72 years. Rankin and Mayo [11] found that in their 55 cases 8 individuals were under 40 years of age. The most common incidence was in the sixth decade, there being 4 cases in this group.

In all previous series it has been said that malignant tumors of the small intestine are a disease of males. In this present group, however, both sexes were attacked with equal frequency.

TABLE I

Résumé of Cases

Case No.	Age	Sex	Clinical features	Site of tumor	Gross description	Metastases	Microscopic diagnosis
	yrs.						
A–96–153	57	M	Vomiting 2 wks., previous malaise, anorexia, constipation, no jaundice	Jejunum	Encircling mass obstructing lumen. Cauliflower growth, central ulceration	None	Slowly growing adenocarcinoma, cells of cylindrical type
A–07–22	37	F	Vomiting 8 mos., weakness, dyspnea, marked anemia 2 mos.	2.5 cm. from pylorus	Encircling mass 5 x 3 x 3 cm., raised necrotic center	Liver	Rapidly growing, poorly differentiated adenocarcinoma, cells of spheroidal type
A–17–109	56	M	Vague abdominal pain 2 mos., anorexia, vomiting, constipation. Jaundice 1 mo. Loss of 25 lb. in 3 mos.	10 cm. from pylorus	Large tumor mass involving 1st and 2nd part of duodenum, tumor presses on common duct	Lung, left kidney, adrenal	Slowly growing, well differentiated adenocarcinoma, cells of cylindrical type
A–20–38	61	F	Vomiting unassociated with pain 1 yr. Jaundice 1 mo.	1st part of duodenum	Ulcerated area 3.5 x 3.5 cm. Base thickened, scarring of serosa	Falciform ligament, retroperitoneal and mesenteric nodes	Moderately rapidly growing adenocarcinoma, cells of cylindrical type
A–26–89	50	F	Generalized abdominal pain 3 mos. Gradual constipation, no vomiting. Loss of 40 lb. in 1 yr.	Upper jejunum	Several small, raised, reddish brown areas on mucosal surface	Mesenteric nodes	Slowly growing, well differentiated adenocarcinoma, cells of columnar type
A–27–288	30	M	P.G.E. for perforated ulcer 4 yrs. ago. Dyspnea, weakness 2 mos. Right upper quadrant pain	Junction descending and transverse duodenum	Villous-like mass 3 x 3 cm. Tumor soft throughout, necrotic in few areas. Ampulla opens 2 cm. above	Mesenteric nodes, liver and peritoneum	Slowly growing adenocarcinoma, cells of columnar type

TABLE I (*Continued*)

Case No.	Age	Sex	Clinical features	Site of tumor	Gross description	Metastases	Microscopic diagnosis
A–31–72.....	yrs. 65	M	Weakness 2 yrs., generalized abdominal pain and diarrhea 4 mos. Loss of 15 lb. No vomiting	20 cm. from pylorus	Ulcerating tumor area 3 x 3 cm. connecting with cystic mass 15 x 15 cm. near head of pancreas containing necrotic débris	None	Slowly growing leiomyosarcoma, tumor composed of spindle cells with oval nuclei, few coarse fibrils seen, tendency to coarse whorl formation
A–32–188.....	70	F	Weakness, generalized abdominal pain several mos. Severe abdominal pain 3 days	2nd part of duodenum	Polypoid mass with many eroded pits on surface. Pancreas negative	None	Rapidly growing leiomyosarcoma, 3 to 4 types of tissue present with smooth muscle predominating, tumor growing in alveolar arrangement
A–35–11.....	50	F	Loss of 50 lb. in 1 yr. Obstipation and vomiting 3 mos.	2nd part of duodenum	Mass 5.4 x 5.4 cm. with central ulceration extending into muscularis. Peripheral soft gray fungoid masses. Ampulla opens at summit of one of these	Nodes about head of pancreas, lesser curvature of stomach	Slowly growing, well differentiated adenocarcinoma with many areas of colloid degeneration, cells of columnar type
A–35–217.....	72	M	Abdominal pain, vomiting, signs of intestinal obstruction 3 wks. Increasing jaundice and acholic stools 2 wks.	2 cm. from pylorus	Crater-like ulcer 2 cm. long with firm gray margins projecting above surface as small nodules. Base of ulcer shows tumor extending into wall and projecting into common duct	Liver, lung, retroaortic nodes	Slowly growing, well differentiated adenocarcinoma, cells of columnar type

Of the 2 cases of sarcoma it will be noted that in each case the tumor arose in the second portion of the duodenum. At autopsy, one was seen to be a small local mass, and the other had eroded through the wall and produced a cystic cavity near the head of the pancreas. It is interesting to note that there was no obstruction to the biliary apparatus in either case. Histologically, both tumors were rapidly growing and arose from smooth muscle.

Of the 8 cases of carcinoma, 6 were primary in the duodenum (of which 3 were in the parapyloric position), and 2 were primary in the jejunum. Grossly, the bulky, polypoid stenosing type predominated over the annular ulcerated growths by a ratio of 3:1. Involvement of the biliary apparatus with resulting jaundice was present in 3 cases. Histologically these tumors were all adenocarcinomas.

The polypoid type is most frequently composed of cylindrical cells. These cells are large, possess a faintly acidophilic cytoplasm and have a large, oval, pale vesicular nucleus. Occasionally a definite ciliated border is seen. Mitotic figures are common and there is often a moderate degree of pleomorphism. Attempts at differentiation are normally present, but the tumor may show well defined glands or only a few ill defined acini. Secretory activity is common, as evidenced by vacuolization of the cytoplasm and the presence of mucin in many alveoli. True tumor giant cells are often seen in the more rapidly growing tumors and fairly large nucleoli are present in this type. The supporting stroma is usually delicate and scanty. The degree of vascularity is not striking.

The ulcerated type of lesion is usually composed of spheroidal cells which possess relatively large vesicular nuclei often containing nucleoli and a rather scanty amount of cytoplasm. This group is usually of a higher grade of malignancy and exhibits many mitotic figures, extreme pleomorphism, and frequent tumor giant cells. Occasionally this group is medullary or scirrhous in nature.

Metastases are fortunately a late manifestation and usually follow lymphatic drainage. In most reported series they occurred in the regional nodes, pancreas, liver and lungs, in relative order of frequency given.

In the series reported here no metastases were found in the cases of sarcoma although they are said to be an early manifestation. Of the cases of carcinoma, metastases were present in all but 1 case and were widespread. The most frequently involved structures were the

liver and the mesenteric and retroperitoneal nodes, which were each invaded in 3 cases. The lungs were the site of metastases in 2 cases. The kidney, adrenal, falciform ligament and peritoneum were each involved in 1 instance. One interesting feature is the lack of pancreatic metastases in this group. This emphasizes the necessity of carefully excluding primary carcinoma of the pancreas and this factor may explain the variation of incidence noted in other reported series.

Discussion

Although no cases of lymphosarcoma were found, they will be discussed briefly. Lymphosarcoma of the intestine may be primary or secondary. It usually starts in the lymphoid follicles but may arise independently of them. The tumor soon extends into and along the submucosa and muscularis mucosae, then into the mucosa and muscularis, but rarely into the serosa. This infiltration of the wall and nerve plexuses often results in extreme thinning and aneurysmal dilatation with perforation occasionally the end result. Stenosis is less common and depends on the degree of fibrosis present. Metastases to the regional mesenteric lymph nodes occur early and, late in the disease, there is hematogenous dissemination with the liver, spleen and kidneys most commonly involved. Microscopically these tumors are of the lymphocytic or reticulum cell type.

When these cases of lymphosarcoma are excluded it is found that fibrosarcoma rarely originates in the small intestine. The most common site is the lower ileum, especially the ileocecal region. Grossly this type of tumor is usually circumscribed or bulging with the central portion ulcerated or necrotic and the periphery covered with mucosa. It generally develops in the submucosa and soon invades the muscularis mucosae and the muscularis but also tends to spare the serosa. Stenosis usually occurs but aneurysmal dilatation is not infrequent and is again due to infiltration of the wall and nerve plexuses. Histologically the round cell type of tumor predominates, with the spindle cell type next in frequency.

Leiomyosarcoma of the small intestine is also said to be extremely rare. It is usually a well circumscribed, oval or lobulated tumor which projects into the lumen as a mound-like mass with central ulceration, or else infiltrates the entire wall. On section, areas of necrosis or hemorrhage are often present. Histologically, well dif-

ferentiated cells with prominent fibrils, which have a tendency to coarse whorl formation, are characteristics of these tumors. The more rapidly growing tumors are composed of masses of large anaplastic cells in which fibrils are found with difficulty.

Carcinoma is the most common of the malignant tumors primary in the small intestine. Grossly the usual type is a papillomatous or cauliflower-like mass which slowly encircles the wall and produces stenosis. This leads to dilatation, muscular hypertrophy and a chronic catarrhal inflammation of the proximal segment. Other types present deep ulcers with elongated edges and a border composed of soft papillary excrescences.

Infiltration of the submucosa occurs early, especially in the annular type of growth. The muscularis mucosae and muscle coats are more resistant and are not involved until later. The serosa is rarely invaded early in the disease. In long-standing cases adjacent organs are infiltrated, especially the pancreas, forming a large indurated mass. Obstruction of the biliary apparatus also is produced in this manner in a few cases.

Ulceration and secondary infection are frequent and may lead to a fatal peritonitis. Perforation with generalized peritonitis is a rare complication.

The clinical features of neoplasms of the small intestine will be discussed in a general way since they all produce the same clinical picture and are classified solely on a histological basis. The symptoms vary in this condition according to: (1) the site of the tumor; (2) type and grade; (3) incidence and site of metastases; and (4) resistance of the patient. Since the growth occurs in the intestine, the subjective and objective symptoms are chiefly those of obstruction.

Flatulence, pain or distress in the epigastrium following meals, weakness, loss of weight and strength, changes in bowel habit and progressive anemia are common prodromal symptoms. Vomiting of the retention type, jaundice, or an acute attack of intestinal obstruction are the usual presenting symptoms.

Attempts have been made to establish the exact anatomical location of primary duodenal tumors by the clinical picture. In the parapyloric position the symptoms are those of pyloric obstruction with profuse vomiting, soon followed by dehydration, alkalosis, nitrogen retention and hypochloremia.

The most common type, the peri-ampullary, is further subdivided

into three types. If the tumor occurs in the upper part of the second portion of the duodenum, or above the ampulla, the symptoms are the same as the parapyloric type. If the papilla is involved, jaundice is an early or presenting symptom. This is frequently associated with a low-grade sepsis supposedly due to a cholangitis. If the tumor is below the ampulla, bilious vomiting with the presence of pancreatic secretions is the common picture.

The prejejunal type is the least frequent and the symptoms are those of a low-grade intestinal obstruction. This type cannot be differentiated from the less common primary tumors of the jejunum and ileum. The clinical picture is one of recurrent and increasingly severe attacks of nausea, vomiting, lower abdominal cramps, visible and reverse peristalsis and borborygmus. There is often a history of constipation which is increasingly severe and which may alternate with diarrhea. Occasional bloody stools are passed and occult blood is a constant finding.

In about half of the cases the onset was abrupt and the clinical picture a stormy one. The average duration of symptoms before patients entered the hospital was about 7 to 8 months. Several cases presented symptoms for over a year.

The usual roentgen ray findings are dilatation of the stomach, gastric residue without demonstrable gastric lesions, and occasionally dilatation or malformation of the duodenal cap. X-ray studies were done on only 4 of the 10 cases. No intrinsic lesion was found in any case. All showed distortion or displacement of the duodenum and were diagnosed as extrinsic tumors or adhesions.

Summary and Conclusion

1. Ten cases of primary tumors of the small intestine have been studied in an attempt to establish their incidence and the frequency and location of metastases.

2. Two cases of sarcoma and 8 cases of primary carcinoma of the small intestine are presented and the literature is reviewed.

3. Metastases were found in none of the sarcomas. They were present in 7 of the 8 cases of carcinoma and were widespread in every instance. The liver and regional nodes were the most frequently involved structures.

4. Tumors of the small intestine are not so rare as commonly supposed.

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SYPHILIS OF THE GASTRO-INTESTINAL TRACT *

REPORT OF A CASE OF GUMMA OF THE TRANSVERSE COLON WITH REVIEW OF LITERATURE

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In reviewing medical literature dealing with syphilis in general, and more particularly with syphilis of the gastro-intestinal tract, it is necessary to bear in mind certain dates: 1905 saw the discovery of the *Treponema pallidum* by Schaudinn; 1906, the application of the complement-fixation phenomenon to the serum diagnosis of syphilis by Wassermann, Neisser and Bruck [1]; 1910, the first successful use of salvarsan by S. Hata the Japanese assistant of Ehrlich; and 1920 (to quote Carman [2]), "Within a very few years the roentgenological examination of the digestive tract has become an extraordinarily effective and practical aid to gastro-intestinal diagnoses."

Before the discovery of the *Treponema pallidum* the diagnosis of tertiary syphilis was necessarily based on clinical history and results of antisyphilitic treatment. A meticulous study of the histopathology of syphilitic lesions was made, stressing the intimal reaction of the larger arteries, the thromboses of the veins, the plasma cell reaction in the granulation tissue, the formation of giant cells and the survival of elastic fibrils throughout the gumma itself. We now know that these tissue reactions are not in themselves diagnostic of syphilis; they may suggest syphilis as the causative factor but do not constitute incontestable evidence on which to base a diagnosis.

The Wassermann reaction is quite often negative in late tertiary syphilis. As stated by Zinsser,[3] the immunity in syphilis is possibly conferred by an existing though hidden and unrecognized lesion. Roentgenological examination of the intestinal tract is invaluable in localizing obstructive lesions but will not incontrovertibly diagnose their type. Referring to the roentgenological appearance of syphilis of the stomach, Holmes and Ruggles [4] make the statement that "the age of the patient, the history and the laboratory findings must be relied upon for corroborative evidence." A syphilitic individual may

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and does fall heir to the same illnesses as do the rest of us and a positive Wassermann will by no means exclude a malignant condition. To quote Boyd [5] on syphilis of the stomach: "When judged by the rigid standard of histological diagnosis the number of genuine cases becomes very much smaller. . . . Turnbull, of the London Hospital, points out that any of the changes commonly found in syphilitic lesions may also be present in an ordinary peptic ulcer; there may be the same infiltration with plasma cells, lymphocytes and eosinophils, the same endarteritis and even giant cells may be found. The only incontrovertible proof that an ulcer is syphilitic is the demonstration in its wall of the *Spirochaeta pallida*, and this has very seldom been done."

The later editions of standard works on pathology limit themselves to the more commonly encountered syphilitic lesions such as mesaortitis and general paresis. The "Principles of Pathology" by Adami and Nicholls,[6] published in 1909, gives sixty-eight references to syphilitic conditions; the index of the "Pathology of Internal Diseases" by Boyd, published two decades later, has only fifteen such references. The inference is that we are taking it for granted that the modern treatment of syphilis precludes the formation of gummas.

References to syphilis of the gastro-intestinal tract found in the accepted textbooks on pathology, including those of Adami and Nicholls,[6] Delafield and Prudden,[7] and Karsner,[8] differ but little from one another as to the character of the information given.

To quote Adami: "Syphilis of the intestines may be hereditary or acquired. In the hereditary form, the small intestine is perhaps the part most frequently involved, . . . usually the jejunum. . . . The lesions of acquired syphilis are most frequently localized in the rectum, rarely in the colon and small intestine. The common lesion is, however, the gumma. . . . the inflammatory process begins in the submucosa and leads to extensive ulceration. . . . Later, extensive fibrous proliferation takes place, which eventually leads to marked stricture. . . . The condition is twice as common in women as in men."

Kaufmann [9] says: "Syphilis of the intestine is congenital or acquired; the latter is very rare and the congenital form is always part of other syphilitic changes (lungs, bones, etc.) and is infrequent. . . . There appear multiple, bacony, gummatous plaques which disinte-

grate to ulcers resembling those of tuberculosis, but usually less deep. The base is bacony and fibrous. Spirochetae have been found in isolated cases. . . . The infiltrations and ulcers show a tendency at times to become ring shaped . . . and their marked tendency to cicatrize leads to stenosis. . . ."

Karsner states: "Lesions of the intestinal tract in acquired syphilis occur as gummata late in the disease. They affect particularly the rectum, the sigmoid and other flexures as well as other parts of the colon, but are rarely observed in the small intestine. . . . Histologically, the picture may be more or less obscured by secondary infection although the latter is not usually severe. There is the usual central necrotic mass surrounded by endothelial or lymphoid cells, in association usually with well marked chronic inflammation of both arteries and veins which may go on to actual occlusion."

Several of the statements from the textbooks just quoted do not agree with the findings in case reports gathered from medical literature. Among 13 cases of syphilis of the gastro-intestinal tract that I have assembled (including my own), 1 was of the stomach, 8 were of the small intestine and 4 of the large intestine. Neither of the 2 cases of syphilis of the colon was of a flexure. None of the references I consulted in my effort to secure reliable data relative to syphilis of the gastro-intestinal tract has considered Durand-Nicolas-Favre's disease as a possible causative factor of stricture of the rectum. For a brief though comprehensive review of lymphogranuloma inguinale the reader is referred to the article by Cormia.[10]

Of all authorities on syphilis none shows the keen insight into the disease shown by Fournier [11] and this is the more remarkable when we consider that the "Traité de la syphilis" was published in 1901. Fournier states: "I believe that in my career I have not seen more than a dozen cases of syphilis of the intestines. Possibly many are unrecognized because we pass them by, believing them *a priori* to be hardly possible. Syphilis of the intestines occurs during the tertiary stage. The small gut is more often involved than the large; sometimes both large and small are involved simultaneously. Sometimes the lesion is single, more often multiple. Coexisting pathology includes peritoneal adhesions, ulcers of the stomach, lesions of the liver, spleen, kidney and lung, mesaortitis and endarteritis, amyloid infiltration, and so on. Perforation of a syphilitic lesion with peritonitis may complicate. Symptoms: A severe chronic diarrhoea

resistant to all (non-specific) medication." Fournier's description of the "general evolution of the gumma in four acts," the third act where "the gumma ulcerates and then eliminates its central core," is classical.

Fraenkel's [12] article on syphilis of the small intestine, published in 1910, has two photomicrographs which illustrate the histopathology of the lesion. The captions call attention to "an especially evident miliary gumma." To me the "body" referred to is a perivascular lymphocytic infiltration, not necessarily syphilitic. The "phlebosclerose" may be encountered in any tissue the site of an inflammatory reaction and is nature's method of shutting off the venous circulation in an area of inflammation. The intimal reaction on the part of the larger arteries is an obliterative endarteritis and is not necessarily syphilitic.

Wile [13] (1921) quoted Oberndorfer [14] as having collected 23 cases of authentic intestinal syphilis. Of Oberndorfer's 23 cases, 16 involved the small intestine, 2 cases involved both the small and the large intestine, 1 occurred in the ileocecal region, and 4 in the large intestine. He stated that the largest number of cases of intestinal syphilis involves the small intestine and the jejunum is the part most frequently involved.

McNee's [15] (1922) article on syphilis of the stomach is illustrated by plates showing the gross appearance and photomicrographs demonstrating *Treponemata pallida*, the intimal reaction of the larger arteries and the perivascular lymphocytic infiltration. The article is refreshingly conclusive compared with other case reports. McNee states: "The occurrence of achlorhydria in the gummatous variety of syphilitic ulceration of the stomach, in contrast to the results of analysis in round ulcer, has attracted attention . . . and tends to add support to an erroneous diagnosis of carcinoma. . . ." The effects of antisyphilitic treatment in gastric syphilis are difficult "to deal with adequately since the clinical diagnosis is so rarely made with accuracy. It is certain, however, that cases have occurred associated with the presence of a large mass in the epigastrium, in which very rapid cure, with gain in weight and removal of cachexia, have occurred in a few weeks after anti-syphilitic treatments." The case reported by McNee was that of a clerk, aged 57 years. The clinical symptoms were, "pain in the chest and abdomen, and constipation alternating with bouts of diarrhoea." He had lost "four stone in

weight" during 6 months and was pale and emaciated. Gastric analyses showed the absence of free hydrochloric acid and the presence of lactic acid. Hematemesis occurred twice. Since there appeared so little doubt of a malignant condition the Wassermann reaction was not done. The patient died of perforation with resulting general peritonitis. The autopsy revealed "a remarkable condition" of the stomach, "which at first sight appeared to fit in with diagnosis of gastric carcinoma of scirrhous type." In one block only (of eight blocks selected) "spirochaetes were discovered in great numbers penetrating deeply in the actively growing granulomatous tissue." No giant cells were seen in any of the sections examined. McNee points out that "the lesion may be seen at various stages, the centre of the ulcer being almost healed and transformed into scar tissue" to "the active stage of granulation tissue formation."

Upcott-Gill and Jones [16] (1924) report an example of "very early gumma of the ileum," in a male, aged 45 years. The Wassermann was positive. Exploratory laparotomy revealed "a thickened segment of the lower ileum, 3 inches in length, lumen almost stenosed." No resection was made but the patient was given an intensive course of antisyphilitic treatment, following which his condition improved. The diagnosis was made: (*a*) by ruling out dysentery, tuberculosis and newgrowth, and (*b*) by the positive Wassermann reaction and therapeutic tests.

Riggs [17] (1925) reported a case of syphilis of the jejunum in a white male aged 68 years. The Wassermann was negative. X-ray examination revealed "obstruction of the transverse colon near the splenic flexure." Laparotomy revealed "a transverse, encircling ulcer of the jejunum located about 2 ft. from the ligament of Treitz." No spirochetes were demonstrated.

Wahlberg [18] (1926) reported the case of a female, 59 years of age. Syphilis had not been considered as she had had four healthy children and the Wassermann reaction was negative. She developed general peritonitis following perforation of an ulcer of the jejunum. Autopsy revealed multiple syphilitic ulcers of the stomach and jejunum. *Treponemata pallida* were not demonstrated.

Maingot [19] (1927) reported the case of a female, 46 years of age, who complained of abdominal pain, intractable diarrhea and loss of weight. The Wassermann was positive and furthermore she had had two miscarriages. A short intensive course of antisyphilitic treat-

ment produced no amelioration of the symptoms and an exploratory laparotomy was performed. A stricture involving the middle third of the descending colon was found. The strictured segment was 14 cm. in length; the lining surface was dark gray and thrown into a series of irregular folds and bosses. The constricted segment was excised but the patient died 1 month later. Microscopic examination of the operative material showed "masses of plasma cells and giant cells; no evidence of sarcoma, cancer, diverticulitis or tubercle." *Treponemata pallida* were not demonstrated.

Perry [20] (1927) cited the case of a male, aged 58 years, who complained of abdominal distress of 7 months duration, with colicky pain appearing suddenly and dying away gradually, accompanied by "much rumbling of the intestines." There was no melena. X-ray examination suggested obstruction of the ascending colon. Operation showed an annular constriction, hard and ring-like, involving the lower jejunum. The pathologist reported: "Almost healed ulcer encircling the lower jejunum; the wall of the intestine at the site of the ulcer is thickened by a tough fibrous tissue." The Wassermann was positive. *Treponemata pallida* were not demonstrated.

Bockus and Bank [21] (1929) discussed upper gastro-intestinal diseases associated with syphilis. The clinical and X-ray postulates are accepted, together with improvement under antisyphilitic treatment and failure to respond to the ordinary regimen. The article is written from the standpoint of the roentgenologist.

Lyles [22] (1930) reported intussusception due to gumma in "a healthy boy age 14 years." There was a history of abdominal pain for 2 days prior to hospitalization and a tender mass was felt in the right lower quadrant of the abdomen. Laparotomy revealed intussusception of the ileocolic type. The wall of the ileum close to the ileocecal valve included "a typical gumma." The Wassermann was negative. *Treponemata pallida* were not demonstrated. If we accept the diagnosis of "gumma" the case falls under the heading of late hereditary syphilis.

Bonne's [23] material (1931) was drawn from the Pathological Institute of the Medical School of Batavia, Java. He reports a case of syphilis of the small intestine in an Indo-European male, aged 36 years. The gross pathology consisted of four isolated, ring-like ulcers of the jejunum with resulting strictures. The diagnosis was based on

the presence in the tissue of "typical giant-cell miliary gummata in the vessel-walls, and plasma cell infiltration." *Treponemata pallida* were not demonstrated.

Ku [24] (1931) reported 4 cases of congenital syphilis of the intestines. He stated that spirochetes were found in only two of the cases. They were found in the mucosa, for the most part subepithelial, "hundreds in a field."

De la Guardia [25] (1931) stated that the intestinal lesions of syphilis range from "slight enteric manifestations to encircling ulcers." He quoted Fraenkel as stating that he found only 3 cases of intestinal syphilis in 19,000 postmortem examinations. De la Guardia reported the case of a Cuban, aged 38 years. The preoperative diagnosis was cholelithiasis. Operation revealed an indurated ulcer, 7.5 cm. in length, encircling the duodenojejunal juncture. The histological examination of the operative material was made by Dr. F. B. Mallory of Boston. The illustrations show giant cell formation. *Treponemata pallida* were not demonstrated.

Tuttle [26] (1932) reported a case of syphilis of the jejunum in a female, a native of Dominica. The admission diagnosis was tuberculous peritonitis. The preoperative X-ray diagnosis was partial obstruction of the transverse colon by malignancy. The Wassermann reaction was positive. Operation revealed "ten fusiform tumors of the jejunum beginning at the duodenojejunal angle and extending down for a distance of 45 inches." The involved section of the jejunum was resected and an end-to-end anastomosis made. Convalescence was uninterrupted. The article is well illustrated and includes photomicrographs of the spirochetes. Warthin (using the Warthin-Starry silver agar technique) found from 50 to 100 treponemata in a single microscopic field.

Ferretti [27] (1933) reported 2 cases of tertiary syphilis of the large intestine; 1 of the sigmoid in a female, aged 45 years, and 1 of the rectum in a male, aged 55 years. Both cases gave positive Wassermann reactions and the diagnoses were based on positive serological findings. The treatment was medicinal.

Buie and Butsch [28] of the Mayo Clinic (1934) reported a case presenting multiple fissures of the anus in a female, aged 50 years. The pupils were fixed and unequal. The Wassermann and Kahn were each positive. Antisyphilitic treatment cleared up the anal condition. No biopsy material was obtained and the diag-

nosis was influenced by the serological reaction and the therapeutic test.

In the case to be reported, the gross specimen (a 12 cm. segment of the transverse colon) was diagnosed as carcinoma, but the density and thickness of the wall of the constricted segment and the firm granular lining surface did not have the gross appearance of carcinoma. When examined under the microscope no evidence of epithelial invasion could be seen. However, infiltration with eosinophilic polymorphonuclear leukocytes suggested an infection and sections were stained by Giemsa but no microorganisms were found except in the necrotic sectors of the mucosa. Lymphocytic hyperplasia was seen in the thickened subserosa and stains by the Ziehl Neelsen technique showed no acid-fast bacilli. As a last resort tissue fragments were impregnated by the Levaditi technique and the first glance through the microscope showed innumerable treponemata.

Report of Case

Clinical History: A. C., a white male, aged 32 years, a soldier with 13 years service (3 years in Hawaii), was admitted to the Walter Reed General Hospital on Oct. 30, 1935. His mother died at 60 years of apoplexy. His father and two sisters died of carcinoma. Two brothers are living and well. There was no history of chancre. The patient's wife was syphilitic and had received antisyphilitic treatment.

On June 6, 1934, the patient's Wassermann reaction was negative, Kahn + +. June 11th the Wassermann was again negative, the Kahn + +. June 20th the Wassermann was still negative, Kahn + + +. June 26th the Wassermann was still negative, the Kahn +. November 15th the Wassermann was ± and the Kahn + +. Antisyphilitic treatment consisted of sixteen doses of neosalvarsan; bismuth salicylate (intramuscularly), three doses; mercury salicylate, two doses; potassium tartrate, five doses. The antisyphilitic treatment was given during the period from June 6, 1934, to Oct. 22, 1935. The spinal fluid was examined during July, 1934, with negative results.

Appendectomy had been performed March 6, 1934. At operation the base of the appendix and about one-quarter of the lower part of the cecum were found to be inflamed and indurated. The stump of the appendix was invaginated with difficulty. Microscopic examination of the excised appendix was interpreted as "an acute catarrhal reaction."

Following appendectomy the patient did well until Oct. 25, 1935, when he complained of dull pain in the right lower quadrant of the abdomen. He was afebrile, and the appetite was poor. The stools were watery in character, but there was no melena. A firm, rounded mass, 10.5 cm. in diameter, was palpated in the right lower quadrant of the abdomen. The mass was movable and tender. The patient was transferred to the Walter Reed General Hospital for observation, and possible surgical intervention on Oct. 30, 1935.

On admission to the hospital he was ambulant and afebrile. He weighed

116 pounds; normal weight 134 pounds. There was slight tenderness over the right lower quadrant and a mass about 10 cm. in diameter was felt beneath the appendectomy cicatrix. An enema reduced the size of the mass. The blood picture was normal.

On October 30th X-ray report was as follows: "The right half of the transverse colon is spastic. There is evidence of a mass close to the hepatic flexure of the colon." On November 4th a second report was as follows: "After the administration of belladonna the spasm of the colon relaxed. There is a large annular carcinoma of the transverse colon, close to the hepatic flexure. Approximately 8 cm. of the gut is implicated" (see Fig. 1).

On November 25th an exploratory laparotomy was done. A mass thought to be carcinoma was found in the center of the transverse colon. This was excised, together with enlarged regional lymph nodes. The cut ends of the colon were inverted and a lateral anastomosis made.

December 27th the patient complained of pain in the right lower chest. He was running a septic temperature. X-ray revealed fluid in the right pleural chink and beneath the right leaf of the diaphragm. A subdiaphragmatic abscess was drained February 5th but the patient died 4 days later.

Histological Examination of Specimen

Gross Appearance of Material Removed at Operation

The specimen consists of a 12 cm. section of colon. The midportion of the excised colon, 5 cm. in length, presents a somewhat thickened wall and a constricted lumen barely admitting the passage of the little finger. The wall of the constricted portion measures from 1 to 2.5 cm. in thickness and is leathery. The cut surfaces of the intestinal wall show a complete loss of architecture and present a glistening, homogeneous, pale gray appearance. The relatively thinner sectors of the involved intestinal wall show a thickened subserosa and submucosa and here the muscularis propria is visible, pale brown and edematous. The lining surface of the above described, annular, cuff-like constricted section of the colon presents a gross appearance coinciding with the microscopic findings: (*a*) there are scattered small nodular areas; the free surfaces of the nodules are raised and covered with necrotic mucosa which is friable and easily eroded by the examining finger; the nodules correspond to the gummas seen microscopically. (*b*) There are irregularly outlined areas presenting a finely granular free surface, which correspond to the sectors of the free surface and which are bare of mucosa and composed of exposed scar and granulation tissue. (*c*) Smooth surfaced, yellowish gray areas showing exaggerated normal markings represent the sectors of the lining surface of the constricted portion of the intestine which are lined by mucous membrane.

Microscopic Examination

Serosa: Attached to the free surface of the serosa is a small amount of an acellular, hyalinized fibrinous exudate. The subserosa shows fibrous thickening and sends in broad trabeculae which divide the fat into small compartments. The fibrous trabeculae are edematous and present swollen fibroblasts, histiocytes and mast cells. There is a diffuse infiltration with eosinophilic polymorphonuclear leukocytes and plasma cells, and scattered agminates of lymphocytes surround or are in close proximity to blood vessels. The larger arteries present intimal thickening and eccentric lumens (Fig. 4).

Muscularis Propria: Edema and slightly advanced diffuse infiltration with eosinophilic polymorphonuclears are present.

Submucosa and Mucosa: Three separate pictures are presented. (1) The gumma is represented by an irregularly outlined, nodular area of incomplete necrosis; "ghosts" of poorly stained, collagenous and elastic fibers remain. The mucosa of the intestine immediately beneath the gumma is completely necrotic and infiltrated with intestinal bacterial flora. The gumma is separated from the adjacent tissue by a zone of capillary hemorrhage and eosinophilic infiltration. Giemsa stain shows no microorganisms in the zone of eosinophilic reaction. In the inflamed zone some of the larger veins are thrombosed.

(2) Long sectors of the lining surface of the intestinal wall are composed of bare granulation tissue.

(3) Short scattered sectors of the lining surface are covered with mucosa which is markedly compressed, and the lamina propria is densely infiltrated with plasma cells. The mucosa shades out gradually at either extremity without undermining or piling up of its free borders.

Submucosa: The submucosa of the entire section of the involved colon, except where actually the site of gummatous formation, is thickened and consists of granulation tissue. The capillaries include many polymorphonuclear leukocytes and show a piling up of their endothelium. The capillaries of the granulation tissue are for the most part arranged in lines perpendicular to the free surface of the intestine. Between the capillaries are varying numbers of plasma cells and in places these cells are massed about small blood vessels. Scattered agminations of small lymphocytes are seen and at the

edges of the nodules of lymphoid tissue the lymphocytes are replaced by plasma cells.

Giant Cells: No true giant cells are found. There are a few scattered, large mononuclear cells with a faintly staining skeiny cytoplasm. The nuclei of these cells are large, oval and vesicular, and present swollen nucleoli. These cells have the appearance of foamy histiocytes rather than true giant cells.

Treponemata pallida: Levaditi stain (Haythorn's modification [29]) shows in the inner edge of the gumma many treponemata, in places as many as 25 to 50 to the high dry field (Figs. 5 and 6). The treponemata are grouped and scattered between the fibrils of the edematous and hemorrhagic tissue located between the "core" of the gumma and the necrotic mucosa which contains no treponemata.

For a complete description of the morphology of the *Treponema pallidum* (Schaudinn and Hoffmann) the reader is referred to the "Text-Book of Bacteriology," by Ford,[30] pages 966–971. The illustrations show *Treponemata pallida* in the lung and liver of a syphilitic fetus.

The treponemata found in the sections of tissue of the case reported average 6 μ in length and present an average of six short undulations joined at acute angles. They are straight or delicately arched and present pointed or flattened ends.

The technique for staining was modified slightly, leaving gross sections of tissue in the silver solution for 48 hours, and overnight in the pyrogallic acid solution, clearing in anilin oil at 55 degrees C., and removing the oil with benzine.

Autopsy Report

Autopsy (A–1908) was performed Feb. 11, 1936. The body was poorly nourished, the skin pale. The recent laparotomy cicatrix presented a fecal fistula communicating with the lumen of the transverse colon at the site of the operative anastomosis. The transverse colon was united to the abdominal wall by firm fibrous adhesions. At the site of the anastomosis the wall of the colon was thin and pseudomelanotic. Below the transverse colon the greater peritoneal chink was rather dry. The coils of the jejunum were adherent to the hepatic knuckle of the colon by dry fibrinous adhesions and similar adhesions united the coils of the lower ileum to one another. The gastro-intestinal tract showed no other pathological condition. The

anastomosis between the cut ends of the transverse colon presented a large stoma.

There were a few enlarged lymph nodes in the mesentery of the transverse colon. The mesenteric lymph nodes were not palpable.

Over the outer surface of the right lobe of the liver was a subdiaphragmatic abscess cavity about 8 cm. in diameter. The cavity was drained by four rubber tubes through the tenth intercostal space. The liver weighed 1760 gm. and was flabby in consistence. The portion of the right lobe forming the inner wall of the subdiaphragmatic abscess showed distinct fibrous thickening of the capsule. Immediately beneath the thickened capsule the liver substance presented capillary hemorrhages and areas of necrosis. The remainder of the liver showed flat cut surfaces, smooth, glistening and pinkish gray. The gall-bladder and the extrahepatic bile ducts were normal and the portal vein contained fluid blood.

The heart weighed 280 gm. The valves and coronaries were normal. The aortic ring measured 7 cm. in circumference. The aorta was normal: thoracic aorta 5 cm. in circumference, abdominal portion 3.6 cm. No evidence of syphilitic mesaortitis was present.

The penis showed no scarring. The tibiae presented no saber-like deformity.

Sections of the liver stained by the Levaditi method show no treponemata. The necrotic edges of the small abscesses are composed of granular detritus in which are seen innumerable microorganisms of the bacillary type.

Comment

After the operative material from the transverse colon had been examined and treponemata demonstrated, the vermiform appendix was reexamined. The lamina propria of the mucosa of the appendix was found to be densely infiltrated with plasma cells; otherwise the changes were those of a simple retrograde metamorphosis. A section of the appendix was stained by the Levaditi method and no treponemata were found. Reconsidering the case leads to the conclusion that the subjective symptoms originally interpreted as appendiceal and for which appendectomy was performed resulted from partial obstruction of the middle third of the transverse colon, producing an accumulation of fecal material in the lumen of the caput coli and ascending colon: this explains why, during appendectomy,

the "base of the appendix and about one-quarter of the lower part of the cecum were found to be indurated and the stump invaginated with difficulty."

Of the cases of acquired syphilis of the gastro-intestinal tract the author has collected (including 1 of the stomach and 12 of the intestines), in only 3 have spirochetes been demonstrated (stomach, McNee; jejunum, Tuttle and Warthin; and the author's case, transverse colon). In the 3 incontrovertible cases treponemata were present in large numbers, from 25 to 100 per microscopic field, and were located in the granulomatous tissue between the necrotic mucosa and the "core" of a gumma.

Analyzing the above 12 cases of syphilis of the intestines, we find the average age of the patient to have been 44 years. Eight were males and 4 females. The Wassermann was positive in one-half of the cases. The lesions were single in 8 and multiple in 4. The small intestine was involved in 8, the jejunum in 6 and the ileum in 2. The large intestine was involved in 4 cases, 1 each of the transverse colon, descending colon, sigmoid and rectum. Five of the patients with syphilis of the small intestine were operated on and four recovered. Both individuals with syphilis of the large intestine who were operated on died. None of the cases was correctly diagnosed, the preoperative diagnoses having been carcinoma in 9, cholecystitis in 1, and intussusception in 1. One patient died of general peritonitis following perforation of an undiagnosed syphilitic ulcer of the jejunum.

Summary and Conclusions

In the case reported here the Wassermann was negative, the Kahn reaction positive. An interrupted course of antisyphilitic treatment administered before the onset of intestinal symptoms had no retarding action on the development of the intestinal gumma. X-ray showed an annular stricture of the midportion of the transverse colon which was diagnosed carcinoma. Operation revealed a cuff-like thickening of the wall of the colon, leathery in consistence, and measuring from 1 to 2.5 cm. in thickness. Stained by Levaditi's method the tissue revealed many treponemata.

This case will interest students of immunology because it illustrates the reaction of syphilis in an individual who had had no primary or secondary manifestations of the disease and "whose im-

munity mechanism was presumably modified, presenting a fulminating precocious recurrence of an inadequately treated early infection" (Stokes [31]).

In diagnosing the cause of chronic intestinal obstruction the possibility of gumma must be considered. The value of such a correct diagnosis outside of purely professional interest lies in the better prognosis offered the patient although operative treatment is indicated in complete obstruction from any cause. The extreme rarity of syphilitic lesions of the intestine causes us to overlook such a possibility. The Wassermann reaction is of no aid in making the diagnosis and when positive the Wassermann does not rule out a malignant condition. Suggestive symptoms are: (*a*) colicky abdominal pain with intractable watery diarrhea alternating with periods of constipation, and (*b*) the location of the obstruction as shown by X-ray. In syphilis the obstruction is most often of the small intestine and quite frequently multiple; when of the large intestine the obstruction tends to be located between the flexures rather than actually of the flexures, as is the case in carcinoma of the colon.

In stricture of the rectum, especially in women, the possibility of Durand-Nicolas-Favre's disease must be considered.

When searching for the treponemata pieces of tissue for silver impregnation and microscopic examination should be carefully selected so as to represent one of the "bosses" which present on the lining surface of the ring shaped thickening of the intestinal wall.

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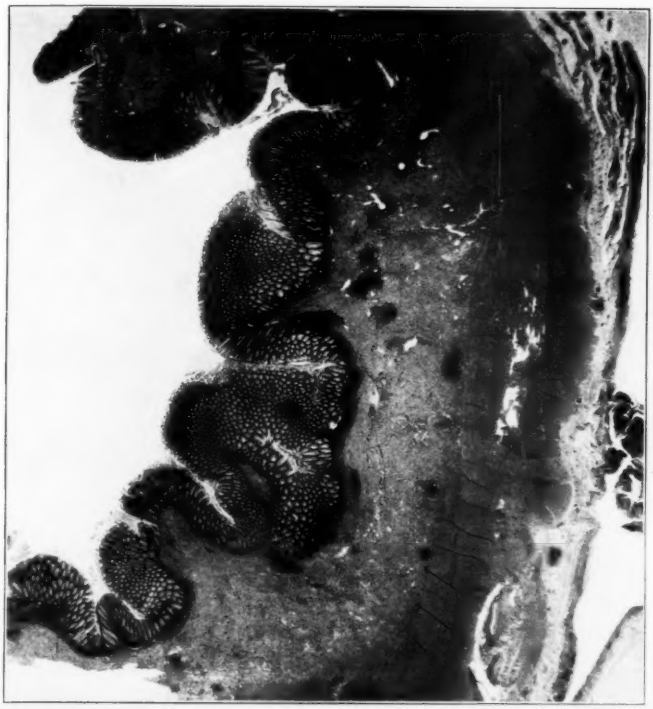
DESCRIPTION OF PLATES

PLATE 7

FIG. 1. Preoperative X-ray showing the location and type of the constriction of the transverse colon.

FIG. 2. The illustration represents the wall of the transverse colon at one edge of the annular constriction. The mucosa is intact, normal markings exaggerated. The submucosa is greatly thickened, the muscularis propria hypertrophied. Scattered throughout the entire wall are small agminations of lymphocytes surrounding or adjacent to the walls of blood vessels. Hematoxylin-eosin stain. × 5.8.



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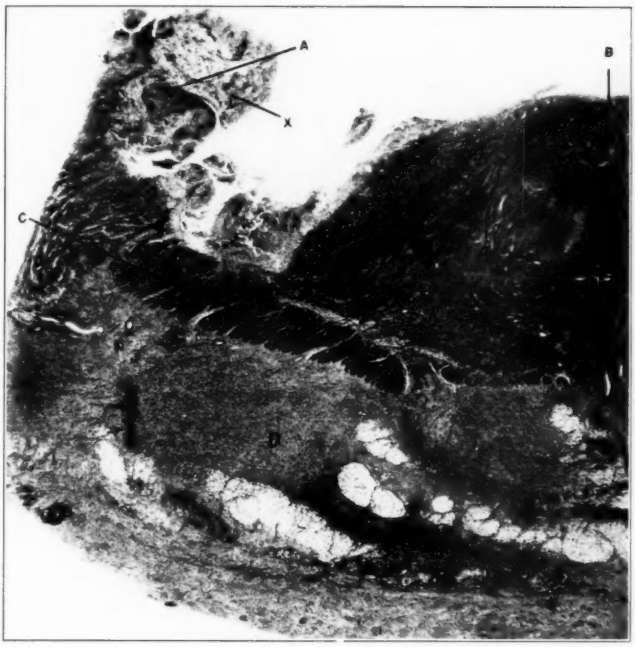
1

Foucar Syphilis of Gastro-intestinal Tract

PLATE 8

FIG. 3. The lining surface (upper margin) includes two gummas occupying the upper left (A) and upper right (B) corners. The gummas are in different stages. "A" is in the "3rd act" (Fournier): the "core" of the gumma is being eliminated and the free surface is ulcerated. Gumma "B" represents an earlier "stage": the "core" is surrounded by a zone of eosinophilic infiltration and the free surface has not broken down. Treponemata are to be found in both gummas, more numerous in "A." "X" indicates area illustrated in Figs. 6 and 7. The muscularis propria (C) is extremely thin and the subserosa (D) greatly thickened. Levaditi stain. × 7.5.

FIG. 4. The two arteries are located in the greatly thickened subserosa of the constricted segment of colon, at a wide distance from the gummas. The arteries show intimal thickening and greatly reduced eccentric lumens. Surrounding the arteries are to be found numerous histiocytes, many of which are basophilic (mast cells). Gram-Weigert stain counterstained with safranin. × 93.75.



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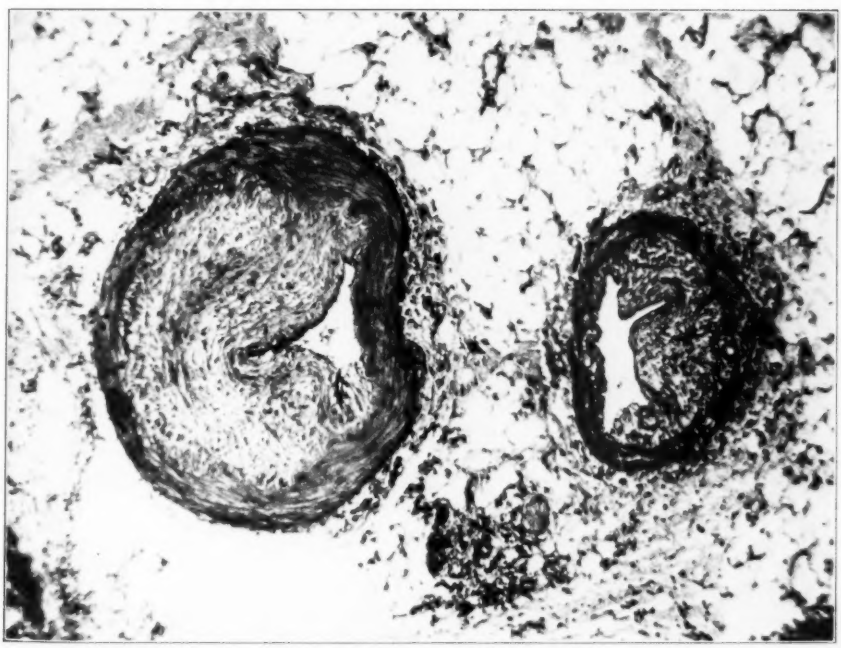

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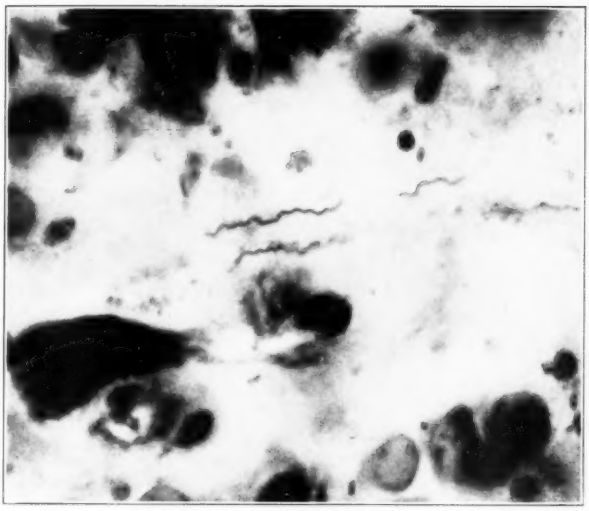
PLATE 9

FIGS. 5 and 6. The area selected is that marked "X" in Fig. 3. The treponemata are located in the granulomatous tissue between the "core" of the gumma and the necrotic lining of the involved portion of the intestinal wall. Levaditi stain, Haythorn's modification. × 1970.



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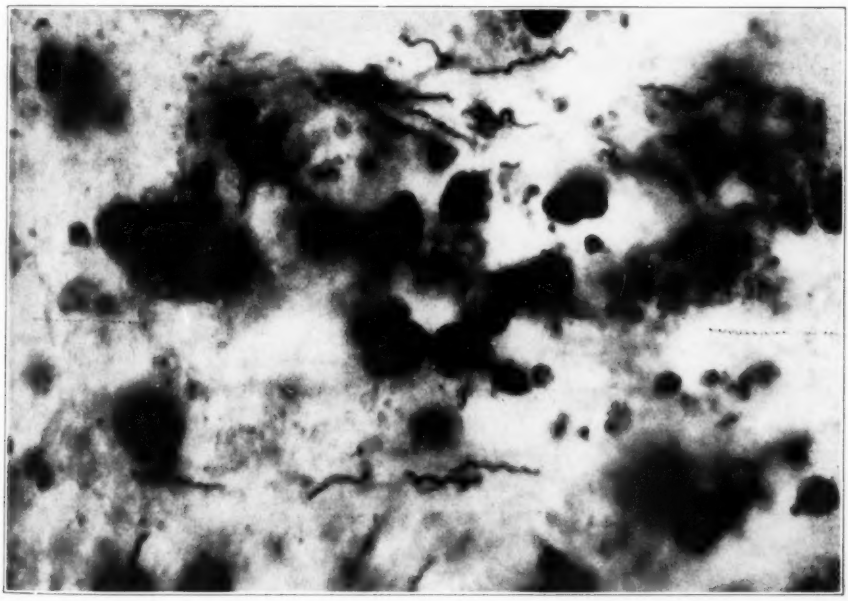

6

ADENOCYSTOMA LYMPHOMATOSUM OF THE SALIVARY GLANDS*

Report of Two Cases

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The tumor with which this paper deals has been described under a diversity of names and its genesis ascribed to a variety of sources, including heterotopic salivary gland tissue in lymph nodes, heterotopic pharyngeal epithelium and branchiogenic rests. For a succinct review of the literature and a comprehensive discussion of the clinical and pathological features of this tumor the reader is referred to the paper of Carmichael, Davie and Stewart.[1] Although uncommon, the tumor is doubtless less rare than the number of reported cases indicates. Carmichael, Davie and Stewart found reports of only 26 cases in the literature, but observed 8 new cases and knew of several unreported ones. Warthin [2] mentions an unreported case sent him by Callender. Hall[3] has recently reported 1 case, and Wood 3 cases.[4] With our 2 cases this makes a total of 41 known cases. An additional case which may belong here was mentioned by Fry [5] in a study of mixed tumors of the salivary glands. Out of 25 cases he described 9 as atypical, and of 1 of the latter he said it required no detailed description: "It is a typical papilliferous cystadenoma, consisting of dilated cyst-like spaces almost entirely filled by papilliferous ingrowths." Two other cases which also may belong here were reported by Steinhardt.[6] His description is too fragmentary to permit one to decide definitely where the tumors belong, but tends to exclude them from this group. He called the 1st case a cystic adenolymphoma, and the 2nd a papillary adenolymphoma. The cystic spaces in the 1st case were lined by a single layer of tall columnar cells, with regions in which the cells were smaller and stratified. The papillae in the 2nd case, for the greater part, were covered by a single layer of cuboidal cells. Both tumors had an abundant lymphoid stroma.

In a study of sublingual and submaxillary glands and uvulae Hamperl [7] observed a peculiar type of epithelial cell, presumably arising as a result of dedifferentiation of glandular and duct epithelium. This type of cell was never seen before the age of 20 years,

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occurred with increasing frequency up to 70 years, and was nearly always present after the age of 70. Hamperl called these cells onkocytes. According to Hamperl,[7, 8] Schaffer[9] had previously called them granular swollen cells, and Zimmermann[10] had called them pyknocytes. These cells resembled those of the adenocystoma lymphomatosum, and in places small groups of them were arranged so as to resemble closely fields in the adenocystoma lymphomatosum. Because of this, Hamperl suggested that they might give rise to these tumors. Jaffé[11] adopted this suggestion and proposed the name "onkocytoma." He emphasized also the presence of secretion capillaries, which had not been mentioned by previous authors. Hamperl stated that onkocytes showed no evidence of secretory activity.

There are several objections to the term "onkocytoma." One is that two of these tumors have been seen in children, respectively 2½ and 12 years of age, while Hamperl never saw onkocytes in individuals under 20 years of age. It is true that Hamperl's series is too small to enable one to say that onkocytes never occur in children, but if they occur they must be extremely rare. Moreover, the abundance of onkocytes in elderly individuals should be accompanied by a corresponding preponderance of "onkocytomas," but there is no such preponderance, the majority of the tumors being first noticed in the fifth and sixth decades. The fact that the number of individuals above 70 years of age is smaller than the number between the ages of 40 and 60 must be taken into account, but does not invalidate this objection. Furthermore, the tumors have been found only in close relation to the parotid and submaxillary glands and at the angle of the jaw, but the cells described by Schaffer, Zimmermann and Hamperl have been found in all three salivary glands, mucous glands of the tongue, floor of the mouth, uvula, pharynx, esophagus, trachea, and serous glands of the tongue. It seems reasonable to assume that if onkocytes give rise to tumors with any degree of frequency the tumors should occur in some of the other sites in which onkocytes are found. The fact that Hamperl saw no encapsulation of the groups of onkocytes is inconsistent with the origin of "onkocytomas" directly in the salivary glands. Arguments against origin of the tumors from onkocytes arising in aberrant salivary gland tissue are not so cogent, since the cells are from the beginning in an abnormal environment. Finally, the term "onkocytoma," although conveniently brief, is not justified since it adds another

name to a list that is already too long, and since the tumor has not been proved to arise from onkocytes.

The term "adenolymphoma" has been applied to this tumor, but seems objectionable in that it exaggerates the importance of the lymphoid tissue at the expense of the epithelial tissue. Without epithelium the tumors would be merely lymph nodes. Since not all of these tumors are papillary, the term "papillary adenocystoma lymphomatosum" should not be applied to the entire group but should be reserved for a subdivision of the larger group. However, the need for classification into papillary and non-papillary types is not urgent.

Since the adenocystoma lymphomatosum has been so well described by Carmichael, Davie and Stewart,[1] only the most essential features will be mentioned here. The tumors usually become apparent in the fifth or sixth decade, and are six or seven times more common in males than in females. Only 2 of the reported cases were malignant. They are found in the region of the parotid and submaxillary glands and at the angle of the jaw, are not attached to the skin, and are usually soft, flattened and bosselated or lobulated. There is a well defined fibrous tissue capsule. The tumors may be solid or partly cystic with papillary structures. They are composed of columnar epithelial cells which form tubular alveoli or clefts and cystic spaces with papillary projections. These are usually lined by a double layer of cells. This arrangement is most evident in thick sections (about 20 microns). The cells of the surface layer average 10 microns in width and 20 to 40 or 50 microns in height, and have their nuclei arranged in an even row toward the free margin. The cells are not ciliated. The basal cells are smaller, irregular, usually less numerous and lie close to the basement membrane. In places the cells are multilayered, but the nuclei of the superficial cells often form a fairly even row near the surface and there are usually many gland lumens at this point. The cytoplasm stains with moderate intensity and contains a fine acidophilic reticulum with innumerable acidophilic granules. The nuclei are spherical or ovoid, 6 to 8 microns in diameter, have a thin nuclear membrane and delicate chromatin network with coarse granules at the nodes. Usually one large nucleolus, or occasionally two nucleoli are present. Indentation of the nucleus is not uncommon. The stroma consists of a delicate reticulum infiltrated by many lymphocytes with formation of

lymph nodules. The material in the cysts consists of granular precipitate with desquamated epithelium, lymphocytes, phagocytes, fat and cholesterol.

Case Reports

Case 1: The patient was a white male, 61 years of age, who was found to have a freely movable tumor at the upper pole of the right parotid gland just anterior to the ear. At operation an encapsulated nodule was found within the gland, but it separated readily from the surrounding tissue.

The surgical specimen was a rubbery, completely encapsulated mass 2 by 1.2 by 1.2 cm. The cut surface was slightly translucent, pale yellowish gray, granular, and showed clefts and small cysts.

Microscopic sections contain numerous cysts less than 1 mm. in diameter and one cyst 3 mm. in diameter. The cysts are lined by the characteristic double layer of epithelium and contain granular débris, some polymorphonuclear leukocytes, fat-laden monocytes and a few cholesterol crystals. In many places polymorphonuclear leukocytes are seen between the epithelial cells. A few coarse papillary processes are seen in some of the larger cysts. There is an abundant lymphoid stroma with many well defined primary and secondary nodules.

Case 2: This patient was a 62 year old male who had first noticed a tumor in the parotid region 4 years previously. At operation an encapsulated tumor was found attached to the parotid gland.

The surgical specimen consisted of a completely encapsulated mass 3 cm. in diameter. The cut surface was yellowish gray and opaque with a few small gelatinous foci at the periphery.

Microscopic sections include a few large cysts containing material similar to that seen in the 1st case, but there are no papillary projections. The epithelial cells are obviously of the same type but form more solid masses. However, these masses contain many small lumens, and the cells about the lumens have the characteristic arrangement. The cells form long, often sinuous cords with irregularly budding outsprouts. There is a dense lymphoid stroma with clearly defined primary and secondary nodules.

In each case the tumor is obviously benign and contains no mitoses. Neither tumor contains ciliated cells.

Discussion

Carmichael, Davie and Stewart say the cells are never ciliated. Warthin [12] stated that in his 2 cases most of the cells were ciliated, but his illustrations do not demonstrate such cells. He further asserted that the first reported cases, those of Albrecht and Arzt,[13] must also have contained ciliated epithelium, although they stated clearly that the cells were not ciliated. There are several possible interpretations of these contradictory statements. One is that Warthin was mistaken and that none of the tumors contains ciliated cells. A second is that there are in reality two different types of tumor, one derived from ciliated cells and the other from non-ciliated cells. It seems unlikely that two different cell types would give rise in the same location to tumors identical except for the presence of cilia. A third is that the tumors form a single group, some containing differing proportions of ciliated cells. This would necessitate origin from cells capable of differentiating into ciliated or non-ciliated cells, and would preclude origin from salivary gland epithelium.

The origin of these tumors is controversial, and must remain so for the present. The most widely held and to us most acceptable theory is that the tumors are derived from heterotopic salivary gland epithelium in lymphoid tissue. There is no convincing evidence that they are of branchiogenic origin, but the occurrence of ciliated cells in such tumors would of necessity indicate origin from a pharyngeal pouch.

Superficially similar tumors, undoubtedly of branchiogenic origin, have been reported by Bonnard [14] and Hickel.[15] Both cases showed abundant lymphoid stroma with prominent lymph nodules. The tumor in Bonnard's case occurred in the parotid region and contained small cysts lined by many layers of squamous cells. In places the cells were two or three deep, and the topmost were of columnar type. Hickel's case was that of a 58 year old female who had had a tumor in the left submaxillary region for 30 years. It contained small cysts lined by two to six layers of stratified squamous epithelium. In places the cells were columnar and formed a single or double layer. Mucous globules were seen in both types of cells. Hickel classed his case with those of Albrecht and Arzt,[13] Glass,[16] and Mazza and Cassinelli,[17] which are of the type discussed by Carmichael, Davie and Stewart. It is apparent that Hickel's case does not

really belong in this group. Origin of such a tumor from adenocystoma lymphomatosum by metaplasia of the epithelium to stratified squamous cells is not impossible but is improbable.

Summary

1. Two new cases of an unusual salivary gland tumor, adenocystoma lymphomatosum, are described.

2. Objections to some of the names which have been applied to this tumor are stated in the hope of clarifying the nomenclature.

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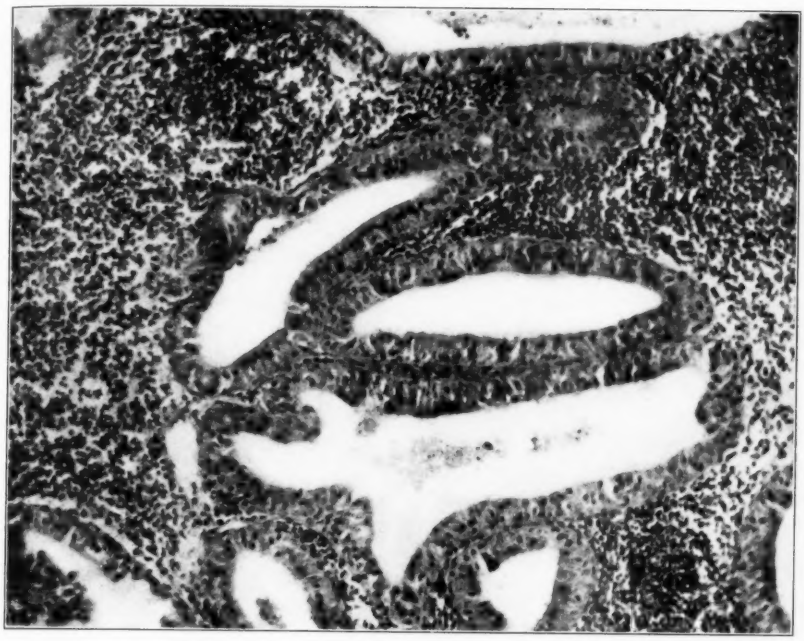
DESCRIPTION OF PLATES

PLATE 10

FIG. 1. Case 1. Arrangement of nuclei in an even row along the margin of the lumen is distinct in some of the cysts. In some places the basal cells are numerous enough to produce the characteristic double row of nuclei. Condensation of lymphocytes into lymph nodules is seen in three foci. Phosphotungstic acid hematoxylin. × 175.

FIG. 2. Case 2. The epithelial cells form much more solid masses but small lumens are not infrequent. The lymphoid stroma is more compact and contains three lymph nodules with distinct secondary nodules. Phosphotungstic acid hematoxylin. × 175.



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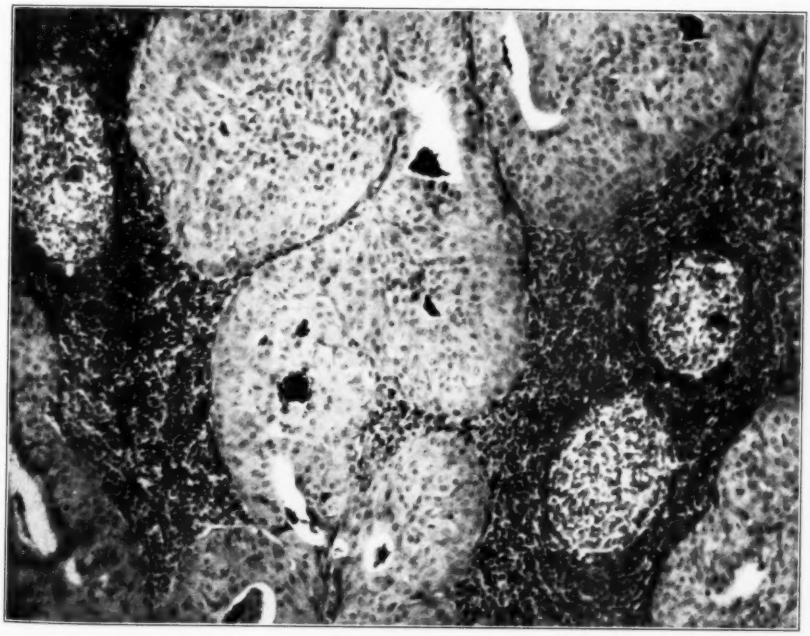


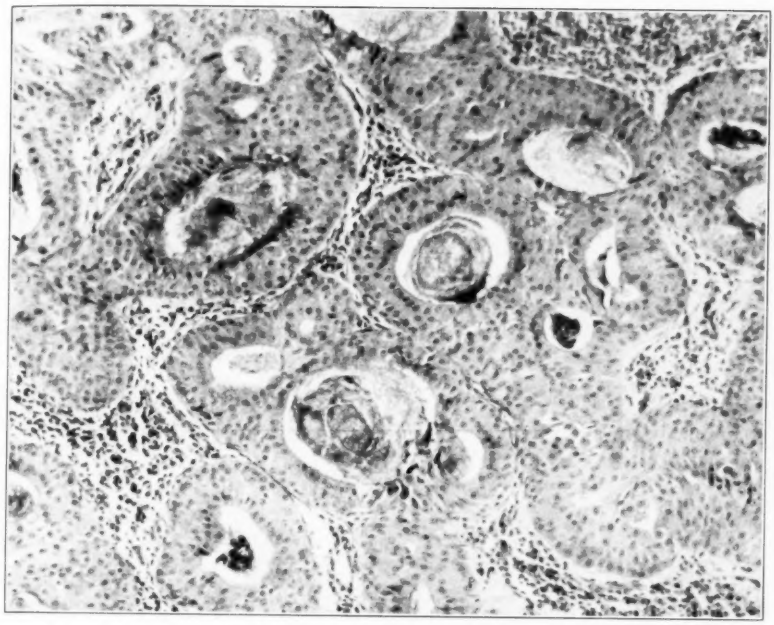
2

Plate 11

Fig. 3. Case 2. This region shows larger glands. Nearly all contain much débris. Note the arrangement of nuclei in an even row about the gland lumens. In many places the glands are lined by two layers of cells. Phosphotungstic acid hematoxylin. × 175.

Fig. 4. Case 1. The basal layer of cells is incomplete, but the arrangement of nuclei in an even row near the apex of the uppermost layer of cells is well shown. Phosphotungstic acid hematoxylin. × 700.

Fig. 5. Case 1. The epithelium in the middle of the field is arranged in two rows for a short distance. Note the two small lumens in the group of epithelial cells at the base of the photograph. Phosphotungstic acid hematoxylin. × 550.



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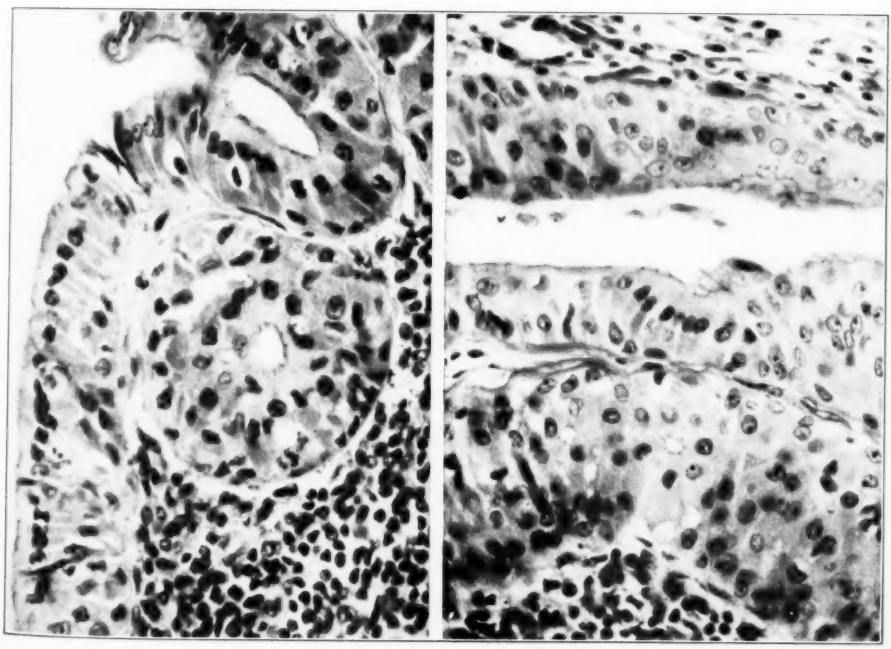

4 5

ANEURYSMAL DILATATION OF THE CARDIAC CORONARY ARTERIES *

Review of the Literature and Report of a Case

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Except for small accessory coronary vessels, anomalies of the coronary arteries unassociated with abnormalities of the heart or great vessels are uncommon. In 1922 Plaut [1] reported a case of absence of the right coronary artery, and in 1930 Petrén [2] reported a 2nd case. Several other cases of "absence" of a coronary artery have been reported, but in all the course of the "absent" vessel was at least approximated by a branch of the other. These cases have been discussed by Petrén,[2] and by Bland, White and Garland.[3] Of interest in this connection are the subsequently reported cases of Born [4] and Hall.[5] In Born's Case I both arteries arose from the right coronary ostium, but shortly after its origin the left artery sank into the interventricular septum and later emerged and followed its normal course. In Hall's case the right coronary artery was short and imperforate.

Origin of the left circumflex branch from the right coronary artery or from the right aortic sinus of Valsalva has been recorded with sufficient frequency to warrant its consideration as a distinct entity. Antopol and Kugel [6] reported 4 such cases, Born mentions 2 (Cases II and III), and Plaut 1. In Plaut's case the right and posterior aortic cusps were replaced by a single large cusp, the right coronary artery arose from the normal site, and the left circumflex branch arose in the middle of the large sinus.

Of more importance are those cases in which one of the two coronary arteries arises from the pulmonary artery. Bland, White and Garland found reports of 8 such cases and added another. Additional cases have been described by Sanes and Kenny,[7] Bartsch and Smekal,[8] Kockel,[9] and Mönckeberg.[10] Wölffhugel [11] described a beef heart in which the right coronary artery arose from the pulmonary artery. In only 2 of the human cases (those of Mönckeberg [10] and Schley [12]) has the right coronary artery been the anomalous one, and in neither was there damage of the myocardium supplied by the

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anomalous vessel. Mönckeberg's case was that of a 30 year old male who died of a fractured skull; Schley's was that of an 81 year old male. Nine of the other human cases form a distinct group, characterized among other things by death within the 1st year of life, and degeneration and fibrosis of the left ventricular myocardium. The remaining 2 cases are those of Abbott [13] and Kockel.[9] Abbott's case was that of a 60 year old female. The right coronary artery had a thick wall and the vessel and its ostium were much dilated. The left coronary artery arose from the pulmonary artery but had the normal distribution. Its wall was thin and Abbott thought the circulation might have been toward the pulmonary artery instead of away from it. Kockel's case was that of a 38 year old male who had had symptoms of heart disease for 10 years and who died suddenly. The left coronary artery was dilated and arose from the pulmonary artery. The left ventricular myocardium showed no degenerative changes. Bland, White and Garland mention 3 instances in which an accessory third coronary vessel arose from the pulmonary artery.

In 1929 Packard and Wechsler [14] collected from the literature 29 cases of aneurysm of the coronary arteries, and described another. These were nearly all of arteriosclerotic or infectious origin. In 1934 Snyder and Hunter [15] collected the subsequently reported cases and added 1 of syphilitic aneurysm.

An interesting, but heterogeneous, group of cases is characterized by dilatation of one or more branches of the coronary arteries. Of these, 7 have occurred in cattle and 4 in man. In some the vessels were cirsoid. Although none of these cases is identical with the case to be described, they are of sufficient similarity to warrant consideration. In 5 of the cattle hearts the dilated vessel communicated with a ventricle (right 4, left 1), but all the animals were healthy.

In Schauder's [16] case, that of a 6 or 7 year old ox, the left coronary artery and its ostium were much enlarged. The circumflex branch and radicles of the anterior descending branch were normal. The anterior descending branch was much dilated and soon left its normal course to enter a multilocular saccular structure measuring 7.5 by 3.8 by 4.2 cm., situated in the interventricular septum. There was no communication with either ventricle. The dilated vessel had a good internal elastica. The wall was thickened, mainly by an increase of the medial musculature, although elastic tissue was also

increased and formed a many layered external elastica. The internal elastica of the sac was poorly defined. The media contained elastic tissue, but little muscle or collagen. Masses of cartilage were present, displacing and compressing the elastic tissue. The wall of the dilated main stem near the aorta was twice as thick as normal, but the constituent elements were present in the normal proportion.

In Reid's [17] case the animal was a 3 year old ox. The left coronary artery and its ostium and anterior descending branch were dilated. The circumflex and other branches of the dilated vessel were normal. The descending branch terminated just above the apex of the heart in a roughly conical, cyst-like structure with base outward and apex on a level with the inner surface of the left ventricle. The wall over the base of the cyst was exceedingly thin. The cyst communicated with the left ventricle by a circular aperture guarded by a valve-like structure composed of an inner fibrous ring 15 mm. in diameter, and an outer fibrous ring 35 mm. in diameter. The rings were connected by a fibrous tissue membrane thickened by several bands running radially between the rings. The wall of the dilated vessel was composed mainly of collagenous tissue with but little muscle and elastic tissue in the media.

Schöndube [18] described the heart of a 7 year old cow in which there was an accessory ventricle formed by a transverse septum across the apical portion of the right ventricle. This contained an opening 4 mm. in diameter. The left coronary ostium and both main branches of the artery were much dilated. The vessels had the usual course and gave off normal branches. At the apex of the heart each vessel showed a region of stenosis and then emptied into a space, which in turn opened into the accessory ventricle. All three layers of the walls of the enlarged arteries were hypertrophic and resembled those of a normal, large systemic artery.

Rubli's [19] case was that of a 62 day old calf. The left coronary ostium was enlarged and situated above the cusp. The diameter of the left coronary artery diminished rapidly, and the vessel gave off normal anterior and circumflex branches. Two cm. from its origin the circumflex branch gave off an anomalous vessel 14 mm. in diameter which, after several angulations and a horseshoe bend near the apex, ascended the interventricular septum posteriorly, and 2 cm. from the coronary sulcus disappeared into the septum, only to bend again and open into the right ventricle 5 cm. above the apex. This

dilated vessel gave off two normal branches which anastomosed with branches of the anterior descending branch. The first portion of the left coronary artery showed increase of elastic tissue at the expense of muscle. The dilated branch showed increase of elastica in the adventitia and less than the normal amount of muscle in the media. The internal elastic membrane was missing except at the origin of the vessel, and here it was incomplete. The right coronary artery was normal except for its origin craniodorsal to the left artery and above the anterior margin of the left posterior cusp. Such displacement of the right coronary ostium has been recorded by several authors and explained by Geipel [20] as depending on the spiral rotation which occurs in the truncus arteriosus and its bulbar swellings.

Joest [21] described an aneurysm of the left coronary artery of a calf's heart communicating with the right ventricle, and Raschke [22] described a cow's heart with an aneurysm of the right coronary artery opening into the right ventricle.

Schlegel [23] described a case of widespread aneurysmal dilatation of both coronary arteries and their branches in a beef heart. The arteries were in places thick walled and narrow, in other places thin walled and dilated, and contained saccular outpouchings. Anastomoses were seen between the vessels, but not in communication with the ventricles. The thickened vessels contained an abundant muscular layer.

Trevor's [24] case was that of an 11 year old female who died of streptococcus septicemia. Five days before death a to-and-fro murmur appeared over the precordium. The right coronary ostium was 1 cm. in diameter and the artery was dilated. The descending branch formed a thin walled aneurysm lying within the right ventricular wall. This communicated with the ventricle by a ragged opening 0.5 cm. in diameter, the margins of which were covered by blood clot. The aneurysm was undoubtedly congenital and rupture probably occurred when the murmur appeared.

Halpert [25] described an interesting arteriovenous communication in the heart of a 54 year old male who died of carcinoma of the stomach. The coronary sinus was dilated to a maximum diameter of 2.5 cm. and was connected to the right coronary artery by a vascular loop 1 cm. in diameter which began at the posterior longitudinal sulcus. The right coronary ostium was 5 mm. in diameter. The right coronary artery was 1.5 to 2 cm. in diameter, elongated and

tortuous. The wall showed atheromatous change with focal calcification. The vessel gave off a normal posterior descending branch and several smaller, apparently normal branches. Microscopically the anastomotic loop showed a structure intermediate between that of an artery and of a vein.

Löwenheim's [26] case was that of a 62 year old female who had had cardiac symptoms for 2 years. The blood pressure was 260/100. The heart was uniformly enlarged and weighed 835 gm. The coronary orifices were normal. Two cm. from the aorta the right coronary artery suddenly dilated to a vessel 5 cm. in circumference, which gave off normal branches. At the interventricular septum posteriorly it ended abruptly as a sac with a narrow connection to a similarly dilated 4 cm. segment of right coronary vein. The dilated part of the vein also terminated abruptly and had normal branches. The layers of the walls of both vein and artery were thickened, but there was an irregularity of distribution of the components, particularly of the muscle. There was no evidence of inflammatory changes.

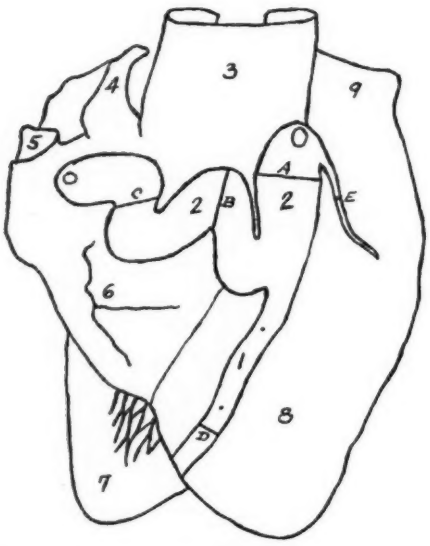
In Kockel's [9] previously mentioned case the right coronary artery and both main branches of the left were greatly dilated and tortuous. The ostium of the right was 6 mm. in diameter. Immediately beyond the ostium the diameter of the vessel was doubled. The left arose from the pulmonary artery and had an ostium 5 by 10 mm. in diameter. The vessels had the normal distribution and did not anastomose with each other or empty directly into veins.

Report of Case

Clinical History: The patient was a 43 year old white male who died of hemorrhage into a brain tumor. No cardiac symptoms had been noted.

Autopsy Report: The heart weighed 380 gm. and the right side was much dilated. The left coronary artery showed moderate arteriosclerosis and the circumflex branch supplied less than the usual proportion of the posterior left ventricular wall. The left coronary ostium was 4 mm. in diameter and the right coronary ostium 5 mm. in diameter. Immediately after its origin the right coronary artery dilated to a circumference of 2 cm. The first branch of the vessel was slightly dilated. The second branch was dilated to a circumference of 2 cm. and with the dilated main stem of the artery formed a tortuous vessel of uniform caliber 13 cm. long, which ran

between the right auricular appendage and the aorta. After an abrupt diminution of caliber at its very end, 8 cm. from the aorta, it terminated in the right auricle through a 1 mm. opening in a soft nodule 4 mm. in diameter, which lay 1.5 cm. superior to the upper



TEXT-FIG. 1. Diagram of anterior superior surface of heart showing right coronary artery. The letters A to E indicate situations from which were taken the sections illustrated in the plate.

1 = main branch of right coronary artery
2 = dilated portion of the artery
3 = aorta
4 = tip of left auricular appendage
5 = superior vena cava
6 = tip of right auricular appendage
7 = left ventricle (internal surface)
8 = right ventricle
9 = pulmonary artery

margin of the foramen ovale. At a point 2.8 cm. from the aorta the main stem of the vessel continued in its normal course as an artery 1 cm. in circumference which, because of the difference in caliber, appeared to be merely a branch of the dilated sinuous vessel. Its branches were normal and it supplied somewhat more than the usual portion of the posterior left ventricular wall. A few atheromatous

plaques were present in both normal and dilated portions of the artery. The variation from the usual distribution of the terminal portion of the left circumflex and right coronary arteries was no greater than is seen in about 20 per cent of all human hearts.

Microscopic Examination: Microscopically the myocardium is not remarkable. The intima of the left coronary artery shows atherosclerosis with focal calcification. The internal elastic lamella is reduplicated and in places is broken. The elastic tissue and muscle of the media are normal except beneath the largest intimal plaques, where there is considerable thinning of the media. The outer portion of the media contains an abundance of elastic tissue forming a broad internal elastic lamella (Fig. 6).

The right coronary artery distal to the dilated tortuous portion shows intimal atherosclerosis, reduplication and focal breaking of the internal elastic lamella, a normal media, and well defined external elastic lamella (Fig. 4). The first branch of the artery shows moderate, uniform intimal thickening, reduplication of the internal elastic lamella, which is broken in a few foci, normal media, and a well defined external elastic lamella which is thinned in a few foci (Fig. 5).

The main stem of the right coronary artery between its first two branches shows slight, uniform intimal thickening. The internal elastic lamella is not reduplicated, but is thoroughly fragmented and contains large gaps. The elastic tissue of the media is diminished in places and many of the fibers are nearly straight. The muscle appears normal. The external elastic lamella shows some thinning and fragmentation (Fig. 1).

The dilated second branch shows slight intimal atherosclerosis. The internal elastic membrane shows some reduplication and much fragmentation, with large gaps in the lamella in some segments of the artery. There is very little elastic tissue in the media and some of the fibers are nearly straight (Fig. 2). The muscle cells in some places are hypertrophic and in places are grouped in bundles with intervening bands of collagen (Fig. 3). In all sections the external elastic lamella is thin and broken and in some places it contains large gaps.

Discussion

The distribution of the dilatation of this vessel and its emptying into the right auricle, together with absence of convincing evidence

of any former infectious process, indicates that the anomaly is a congenital one. The reason for the dilatation is not so obvious. Deficiency in the elastic tissue is the most significant microscopic abnormality. Whether or not dilatation of the vessel occurred because of deficiency in the quality or quantity of the elastic tissue is problematical, but not improbable. It is, of course, possible that destruction of the elastica is a secondary change.

Communication of the artery directly with the right auricle is best explained on the basis of Grant's observations on a child's heart [27] in which blood-filled spaces in the ventricular muscle communicated freely with the coronary vessels and the cavity of the ventricle, and on his study of the development of the coronary vessels in rabbit embryos.[28] The latter study disclosed the presence of endothelial outgrowths between the forming auricular and ventricular myocardial trabeculae. These outgrowths extend out to the epicardium and develop as vessels, which in the auricles ultimately connect with the auricular branches of the coronary vessels and form the thebesian vessels. In the ventricles they join each other and the ventricular branches of the coronary vessels. For the most part, these intertrabecular spaces are reduced to capillaries, but persist as an integral part of the coronary circulation. Abnormal development of one of the auricular outgrowths would produce communication of the auricle and coronary artery, as seen in our case, but the reason for the abnormal development is obscure.

Summary and Conclusion

1. A case of cirsoid aneurysm of the right cardiac coronary artery communicating with the right auricle is described and explained as a congenital anomaly probably due to deficiency in elastic tissue. Communication with the auricle is attributed to development of a fetal communication which is ordinarily reduced to capillary size.

2. The literature concerning certain anomalies of the coronary arteries is reviewed.

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DESCRIPTION OF PLATES

Plate 12

All photographs were taken at a magnification of 150 diameters. The sections were stained with Verhoeff's elastic tissue stain.

Fig. 1. (A) Main stem of right coronary artery. The internal and external elastic lamellae are broken, the elastic tissue of the media is diminished and some of the fibers are straight.

Fig. 2. (B) Second branch of right coronary artery. The internal elastic lamella is broken and there is hardly any external elastic lamella. There is but little elastic tissue in the media and the fibers are straight or only slightly wavy.

Fig. 3. (C) Second branch of right coronary artery. There is a distinct internal elastic lamella and the intima contains much elastic tissue. The external elastic lamella is broken. The media contains only a few short elastic fibers. Hypertrophy of the muscle fibers in the outer portion of the media is manifest.

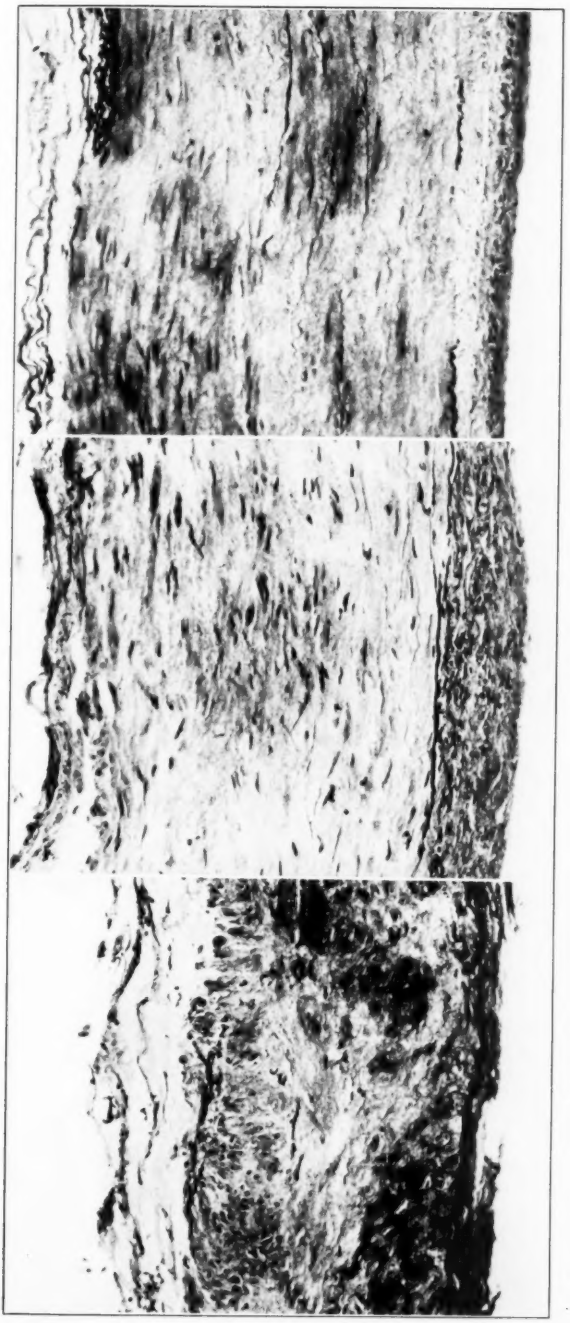

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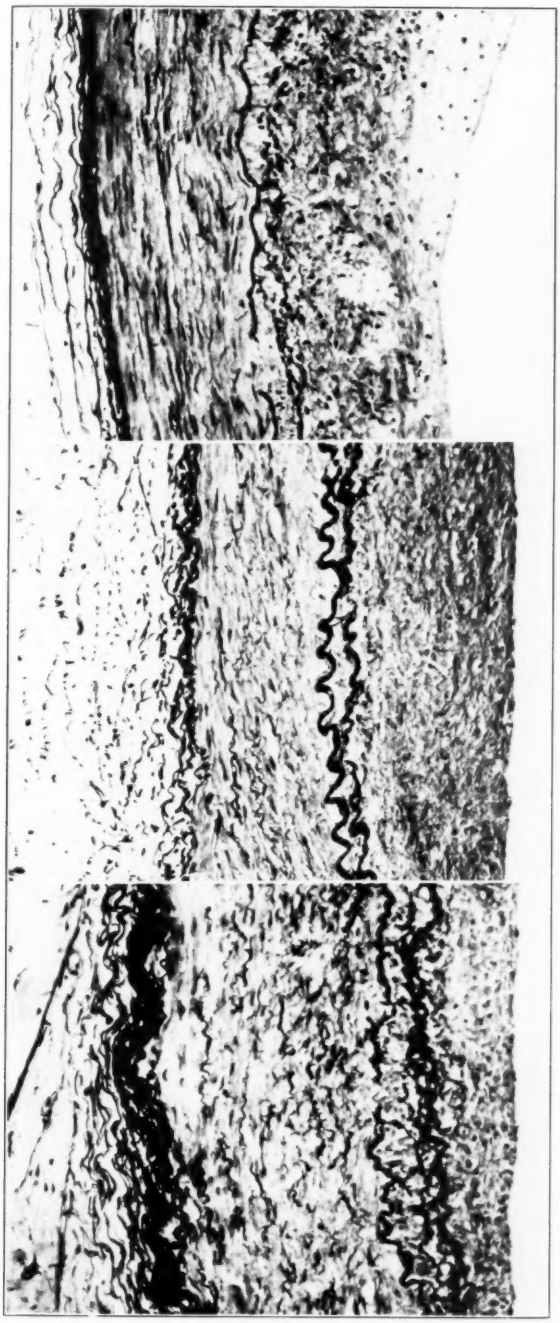
PLATE 13

FIG. 4. (D) Main stem of right coronary artery. The intima shows atherosclerosis. The internal elastic lamella is broken and reduplicated. There is a broad external elastic lamella and the elastic tissue of the media is abundant.

FIG. 5. (E) First branch of right coronary artery. There is reduplication of the internal elastic lamella and some thinning of the external elastic lamella. The elastic tissue of the media is abundant.

FIG. 6. (F) Left coronary artery. The internal elastic lamella is reduplicated and broken, there is a very heavy external elastic lamella and an abundance of elastic tissue in the media.



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MIXED TUMOR OF THE LACRIMAL GLAND *

Review of the Literature and Report of a Case

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Enlargement of the lacrimal gland may be due to inflammatory change, cystic degeneration, Mikulicz's disease, leukemic infiltration, or to primary neoplasm. Although tumors of any type are rare in this location the mixed tumor is the most common type encountered. According to Pfingst,[1] Fabricius Hildanus reported the first case of mixed tumor occurring in the lacrimal gland in the year 1598. Warthin [2] made the first careful study of this pathological entity and reviewed the literature up to 1901. A few years later Verhoeff [3] reported 5 cases. The cases first described by Warthin were later reviewed by Lane [4] in 1922. Since the publication of an article by Davies [5] in July, 1934, Last [6] has published a case which, including the case recorded in this article, makes a total of 267 cases reported up to the present time.

Clinical Data

The development of a mixed tumor of the lacrimal gland is slow. The globe is usually displaced nasally and there is limitation of motion of the eyeball upward and outward. Lacrimation and exophthalmos are common symptoms and there is usually no pain. Impaired vision is not uncommon in the later stages of the tumor development and proptosis is almost always the rule. The tumor is not palpable until the neoplasm is quite large. Lane [4] stated that recurrence occurred in 20 per cent of cases and that the mortality was 12.63 per cent in the series she studied.

Histogenesis

As regards histogenesis the same problems exist in mixed tumors of the lacrimal gland as in mixed tumors encountered elsewhere about the oral-facial region. According to Last,[6] 90 per cent of mixed tumors occurring about the head and neck are found in the region of the parotid gland. These tumors are also encountered in

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the hard palate, [7, 8] throat,[9] lips, jaws, nasopharynx, pharynx, nasal fossae, floor of the mouth, tongue, and skin of the face and scalp.[8] The theory of endothelial origin first advanced by Warthin [2] has been almost entirely abandoned. Many pathologists believe that the tumor is entirely epithelial. That there is no unanimity of opinion is evidenced from the statements made in comparatively recent articles. Martin and Elkin [10] in 1934 stated that the epithelial theory is generally accepted although not universally so. In the same year Stein and Geschickter [11] presented good evidence that the composition of mixed tumors occurring in the parotid gland is most readily explained on embryological grounds. In January, 1936, Driver [8] stated that "the enclavement or accidental sequestration theory of the origin of mixed tumor is now accepted by many leading pathologists." Davies [5] in 1934 stated: "Birch-Hirschfeld and others present more conclusive evidence favoring the epithelial origin."

Eggers,[7] in an excellent review of the literature and a presentation of 7 cases of mixed tumor of the palate, stated that Warthin and Verhoeff have previously pointed out that the presence of these tumors in the lacrimal gland is evidence against the embryonic displacement theory of development, inasmuch as cartilage also is found in these tumors. However, Eggers believes that the close proximity of the ethmoid cartilage must be considered and therefore that the evidence cited by Warthin and Verhoeff is by no means conclusive.

Benedict and Broders,[12] and New,[9] choose to refer to these tumors as adenocarcinomas of the mixed tumor type. New and Childrey [13] state that these tumors are now generally regarded as adenocarcinomas. There seems to be little reason for discarding the generally used and understood terminology of mixed tumor. In fact there is little reason, either clinical or pathological, for calling these tumors adenocarcinomas. Many perfectly typical tumors of this type not only clinically but from the standpoint of pathology also bear not the remotest resemblance to tumors occurring elsewhere which are recognized as adenocarcinomas. As pointed out by Stein and Geschickter,[11] the most active element of these tumors is an elongated basal cell which is readily transformed into a cuboidal or columnar type. When, as is rarely the case,[14] carcinoma does occur in this type of tumor, it should probably be termed a basal cell car-

cinoma rather than an adenocarcinoma. Stein and Geschickter [11] also point out that it is usually the atypical carcinomas of the parotid that give rise to distant metastases.

Further evidence supporting the embryonic or enclavement theory of the development of mixed tumors occurring about the face and oral region is given in the recent work by Li and Yang.[15] Based on a study of 25 mixed tumors occurring in the face, scalp and oral cavity, Li and Yang present good evidence to show that they represent neoplasms derived from rests formed from the developing ectoderm of the mouth in the case of oral tumors, and in the case of lacrimal gland tumors from the conjunctiva together with the anlage of the lacrimal gland. They also believe that the histological similarities and differences among the mixed tumors closely allied to them are explained by differences in the origin and time of rest formation. McFarland, Ciccone and Gelehrter,[16] taking for granted the accepted proof of the dysontogenetic nature of mixed tumors, present good evidence that basal cell carcinomas occurring about the face belong in this category also, and that both arise as a result of imperfections in the closure of the embryonal facial fissures.

Pathology

The gross and microscopic features of mixed tumor of the lacrimal gland are quite characteristic and conform in practically every respect to mixed tumors occurring in the salivary glands and oral-facial region. The tumor, as it occurs in the orbit, is usually in, attached to or closely associated with, the lacrimal gland. It is usually encapsulated and may vary considerably in size. It is firm and on cut section shows a heterogeneous variegated surface. Most of the tumor is firm, although on cut section mucoid material is commonly seen. Calcification may occur.

The microscopic structure of mixed tumor of the lacrimal gland differs in no respect from that of similar tumors found elsewhere. The tumor is usually described as complex and as containing both epithelial and mesenchymal elements. In every instance it is evident that both the epithelium and the mesenchyma take an active part in the neoplasm, although usually the epithelium seems the more active. According to Stein and Geschickter,[11] the most benign mixed tumors are composed of epithelial elements arranged in definite gland formation with a large amount of connective tissue (often

myxomatous) and of cartilage. The more malignant type, according to them, usually contains less cartilage and connective tissue. They believe that these tumors in recurrent cases show many characteristics of basal cell carcinoma without a tendency to metastasize. On the other hand, Thibaudeau and Burke [14] conclude, after reviewing 66 cases previously reported by Schreiner and Mattick,[17] that the histological picture in no way aids in the determination of the relative malignancy or the clinical outcome. McFarland [18] divides his cases of mixed tumors into three groups: (1) those tumors that are mainly fibrous with little mucous degeneration and no cartilage; (2) tumors that are exceedingly hard and contain a large amount of cartilage; and (3) those that are soft and cellular with transparent trabeculae and mucus. He believes that Groups 1 and 2 are benign, and that Group 3 should be considered malignant. Eggers,[7] in his study of mixed tumors of the palate, states that there is an apparent transition from epithelium to connective tissue but that this apparent merging of stroma is a general phenomenon seen whenever there is invasive growth of epithelium into stroma bathed in an excess of mucinous fluid. D'Aunoy [19] quotes Fraser, Masson and Peyron, and Desmarest and Masson as believing that the parenchymal cells come from normal glands and that the mucoid connective tissue cartilage matrix arises from the epithelium of the tumor itself. D'Aunoy, however, believes that the enclavement theory presents the correct solution of the problem.

Report of a Case

Clinical History: The tumor which forms the source of study for this communication was removed from a white female, 64 years of age, and a known diabetic for 15 years, who was admitted to the Lincoln General Hospital on Dec. 5, 1933, complaining of dimness of vision, diplopia, lacrimation and prominence of the right eye.

She had consulted a physician before admission to the hospital, who had attributed the symptoms to diabetes and suggested a more adequate diabetic regimen. This opinion was corroborated by an ophthalmologist. Early in 1930 she noticed swelling and prominence of the right eye with impaired vision. About this time lacrimation increased and the lacrimal ducts were probed. This caused a decrease in the amount of lacrimation but the vision became progressively worse. These symptoms became slowly progressively worse until September, 1933, at which time she consulted another ophthalmologist who found a soft fixed mass, about 1 by 1.5 cm., located in the region of the right lacrimal gland. This was not tender. There was no apparent loss of ability to move the eyeball, although it appeared enlarged and somewhat displaced downward and medially. Both pupils reacted normally to light and accommodation, and there

was increased lacrimation in the right eye. A diagnosis of lacrimal gland tumor was made and she was advised to consult a radiologist for X-ray treatment.

The patient received two X-ray treatments and a portion of the tumor was removed Dec. 6, 1933. She was discharged from the hospital Dec. 11, 1933, with some improvement of excessive lacrimation but no improvement of vision. She was given 3200 R units of high voltage X-ray therapy.

Her condition remained essentially unchanged in spite of X-ray therapy and she was readmitted to the hospital July 24, 1935, with recurrence of symptoms. Further surgery was advised and a well defined, soft, gelatinous tumor mass was removed from the upper outer portion of the right orbit on July 25th. Since then the patient has been free from symptoms as far as the eye is concerned, although lack of coöperation on her part has made satisfactory management of the diabetic condition impossible.

Histological Examination of Tumor with Discussion

The first tissue removed on July 6, 1933, consisted of three irregular bits of soft grayish tissue, rather mucinous in character, each one of which was less than 1 cm. in its greatest diameter. At the second operation the tumor was intact, measured about 1 by 2 cm., and was surrounded by a definite fibrous connective tissue capsule.

In spite of the time interval between the first and second operations the histology of the two tumor specimens is identical and will be considered together. Blocks of the tumor were fixed in 10 per cent formalin and in Zenker-formol solution and cut at 4 and 7 microns. Sections were stained with hemalum and eosin, Masson's trichrome hemalum-erythrosin and saffron, iron hematoxylin-ponceau-acid fuchsin-aniline blue, and iron hematoxylin-ponceau-acid fuchsin-light green.

The structure of the tumor is typically that of a mixed tumor. Epithelial cells varying from the long spindle shaped basal cell to the cuboidal and columnar cell are arranged in infiltrating strands in some instances and in definite gland formation in others. Where the cells are found in solid masses they tend to be spindle shaped, and where there is a tendency to gland formation they are cuboidal or columnar. Often they are arranged in long, double branching rows which are surrounded by a myxomatous connective tissue. It is noted that wherever there is a tendency to gland formation there are two rows of cells. The row of epithelial cells nearest the lumen is either very low cuboidal or spindle shaped, and the outer row of epithelial cells, or those farthest removed from the lumen, are tall columnar cells. The lumens of these attempts at gland formation are often filled with a solid, structureless, homogeneous pink stain-

ing material. In one section studied, the lumen of one of these glands is filled with large vesicular cells whose cytoplasm is typically granular.

In the hemalum and eosin stained sections several areas give one the impression that there is a gradual merging from the epithelial cells to the surrounding, loosely arranged mesenchymal elements. However, the sections stained with Masson's trichrome stains show that this transition is more apparent than real and in each instance it is found that there is actually a sharp segregation between the epithelial cells and the fibroblastic stroma. A basement membrane is not uncommonly encountered. This is most readily seen in the sections stained with Masson's iron hematoxylin-acid fuchsin-aniline blue.

These epithelial elements are embedded in a loosely arranged mesenchyma which, in most of the tumor, is myxomatous. The individual cells are fibroblasts which, in myxomatous areas, are separated by intercellular fluid. In many areas chondroblasts and adult cartilage cells are found and in each instance there is a gradual transition between these and the myxomatous connective tissue. No bone is seen in these particular sections. Metaplasia, or "protoplasia" as Fried [20] chooses to call it, may be used here to explain this change if the term is used in its modern sense. This modern concept of metaplasia emphatically denies the transformation of a fully developed, well differentiated cell of one type into a well developed cell of another type.[20] Metaplasia, as it is now understood, presupposes differentiation from an undifferentiated mother cell which may produce several types of adult tissue.

The undifferentiated mesenchyma seen in this tumor is identical with the mesenchyma into which the epithelial cells from the embryonic conjunctiva first emerge developmentally.

The lacrimal gland first appears as five to six proliferations of epithelium of the conjunctiva in the upper portion of the outer fornix in embryos of 32 mm. These are at first solid, but show branching at 38 mm. The epithelial cells are at first compressed polyhedral basal cells, and later at 50 mm. they form two layers, a basal and a secreting layer. As is true in the epithelial elements of mixed tumors, these tubules are not sharply segregated from the surrounding mesenchyma. The solid masses of spindle shaped basal cells resemble the epithelial cells making up the first proliferating

buds of the anlage of the lacrimal gland and the more differentiated tubular elements imitate very strikingly the embryonic ducts seen soon after the lumen forms and the branching occurs.

Consideration of the phylogeny of the lacrimal gland explains in a measure the existence of mixed tumors in the lower lid and other portions of the orbit. In the amphibian there is a glandular structure which travels developmentally along the lower lid toward the lateral angle. Among the reptiles some have a glandular mass at each angle of the lower lid. In the serpent the lateral gland is lacking but the medial gland, or gland of Harper, opens into the mouth, thus taking on the functions of a salivary gland.[21] In tracing the structure phylogenetically it migrates along the lower lid to the outer angle and in man appears in the upper lid.

Although there is some argument as to whether the epithelium from which the salivary glands arise is entodermal or ectodermal, there is no question about the character of the epithelium from which the lacrimal gland arises. It is ectodermal. The precisely similar nature of mixed tumors arising in other salivary glands to those occurring in the lacrimal gland makes it seem probable that the epithelium from which the other salivary glands arise is also ectodermal.

Squamous epithelium was not encountered in this particular tumor, but it is not uncommonly found and is readily explained when one considers that the squamous epithelium of the conjunctiva, as seen in adult life, is developed directly from the same undifferentiated cell as are the columnar and spindle shaped epithelial cells encountered in the ducts of the lacrimal gland.

Surgical removal of mixed tumors of the lacrimal gland is the logical method of treatment unless the tumor is so large as to make this impossible, in which case radiation therapy either alone or combined with surgery should be used.

Summary and Conclusions

1. Mixed tumors occurring in the orbit and arising either from or in close proximity to the lacrimal gland are rarely encountered.

2. Clinical diagnosis is difficult until the tumor becomes visible or palpable.

3. The gross and microscopic aspects of mixed tumors of the lacrimal gland are identical in every respect with the same tumor which occurs more frequently in the parotid and other salivary glands.

4. Correlation of the histological aspects of this tumor with the development of the lacrimal gland strongly supports the theory that these tumors are developmental, representing misplaced embryonic rests or enclavements.

5. Study of sections stained with Masson's trichrome methods denies the transition between epithelial and mesenchymal elements of the tumor, and clearly demonstrates that both the epithelium and the mesenchyma take an active part in the tumor growth.

6. Evidence is presented that denies these tumors are strictly epithelial.

7. There is no clinical or pathological evidence that these tumors are adenocarcinomas and it is suggested that this term be abandoned as it only tends to add to the confusion already existing in tumors of this group.

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DESCRIPTION OF PLATE

PLATE 14

FIG. 1. Low power photomicrograph showing adenocystic structure. Note the intervening myxomatous stroma. Masson's hemalum-erythrosin-saffron stain.

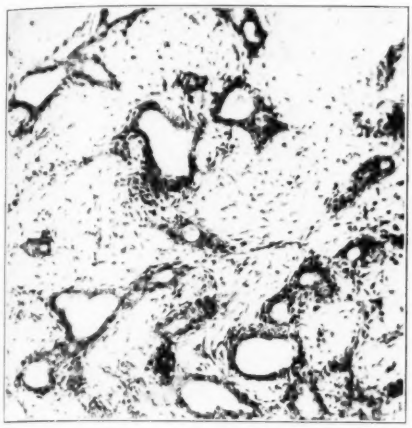
FIG. 2. Low power photomicrograph showing gradual transition from young fibrous connective tissue to cartilage. Note sharp definition between stroma and epithelium.

FIG. 3. Low power photomicrograph showing islands of undifferentiated epithelium embedded in adult collagen. This type of change is often wrongly interpreted as carcinoma.

FIG. 4. Low power photomicrograph of section stained with Masson's iron hematoxylin-acid fuchsin-aniline blue method showing fibroblasts and young cartilage.

FIG. 5. Low power photomicrograph of section stained with Masson's iron hematoxylin-ponceau acid fuchsin-light green method showing sharp line of demarcation between epithelium and stroma.

FIG. 6. Oil immersion photomicrograph showing character of young fibroblastic stroma.



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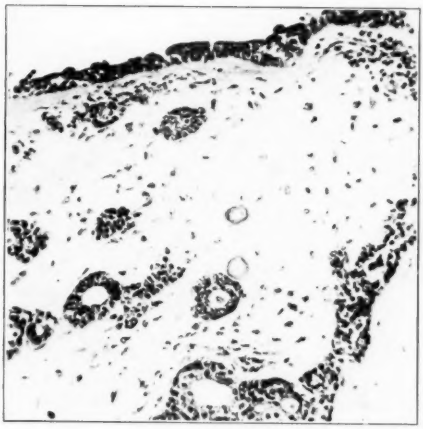

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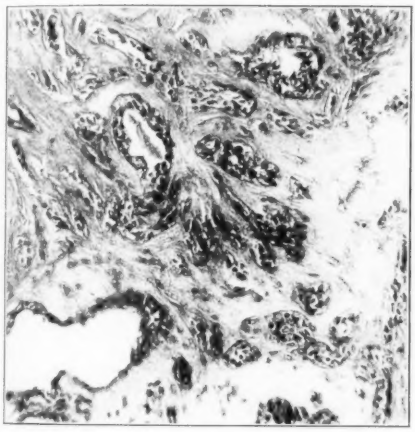

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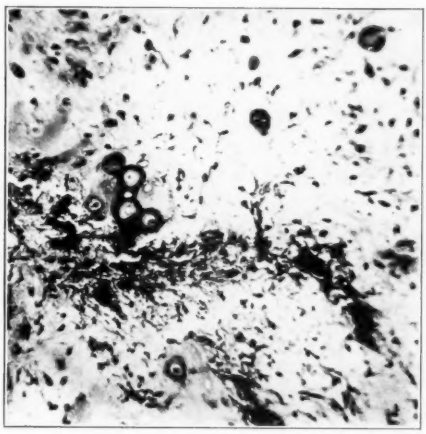

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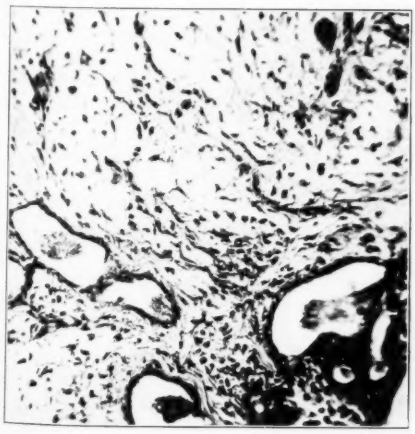

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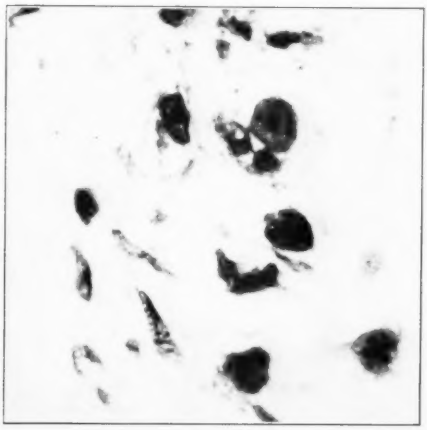

6

Neely

Mixed Tumor of Lacrimal Gland

MALIGNANT LYMPHOGRANULOMATOUS (HODGKIN'S DISEASE) CIRRHOSIS OF THE LIVER *

Report of a Case

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The picture of Hodgkin's disease as predominantly one of lymph nodes is firmly fixed in the minds of those who come in contact with this disease as, indeed, it should be. But many other manifestations have been noted. Thus recently, numerous reports have dealt with Hodgkin's disease of bone, the lungs, gastro-intestinal tract, central nervous system, skin and other organs. The manifestations may be so varied as to warrant the statement that probably no other disease is more protean. The malignant lymphogranulomatous tissue may involve and invade not only the site where lymphoid tissue previously existed, but any non-lymphoid organ. It may produce symptoms by its bulk when it is cellular, and by its contraction when it is scirrhous. Hence, the production of a small cirrhotic liver such as that described in this paper is not to be entirely unexpected.

Among the organs commonly involved in Hodgkin's disease is the liver. In recent reports the incidence of hepatic lesions has varied from 36 per cent in Uddströmers [1] cases to 71 per cent in the report of Symmers.[2] The diseased livers are usually enlarged because of the lymphogranulomatous tissue nodules which they contain. More infrequently they are decreased in size. The specific infiltrates vary in size from those visible only microscopically to large, grayish white or yellowish nodules several centimeters in size. Microscopically the structure usually resembles that seen in the extrahepatic lesions of the same case. It is consequently pleomorphic and may be either scirrhous or cellular. There may be sufficient compression of intrahepatic bile ducts to produce jaundice. The ascites so commonly present in Hodgkin's disease is not necessarily dependent on intrahepatic portal obstruction since it is seen also when the liver is involved only to a minor degree or not at all.

The writer recently studied postmortem an interesting example of an unusual type of liver involvement in Hodgkin's disease. It is

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named most conveniently "malignant lymphogranulomatous, or Hodgkin's disease cirrhosis of the liver." The case is one in which the lymph node disease was of minor importance and well localized, but spontaneously extremely scirrhous in nature. By some untraceable circumstance a delicate but widespread infiltration occurred along the periportal areas in the liver. Here also there was early spontaneous fibrosis of the lymphogranulomatous tissue. The result was an advanced degree of periportal cirrhosis with portal obstruction, but the clinical picture was that of cirrhosis of the liver. At autopsy the liver weighed only 855 gm. and grossly showed a uniform, finely nodular type of cirrhosis not in the least suggestive of the usual liver seen in Hodgkin's disease. Microscopically, however, the changes were recognizable as lymphogranulomatous.

Report of Case

Clinical History: W. B. A., a white railroad engineer, aged 55 years, entered the Illinois Central Hospital in Chicago on Sept. 11, 1935. For 1½ to 2 years he had noticed small, painless, slowly growing masses in the left groin and in the femoral region, and for 1 year "lumps" had been present in the left submaxillary region. These masses underwent spontaneous variations in size. At one time they had been present in the left axilla. The patient had been working until 3 weeks before admission to the hospital, but had been growing progressively weaker during the previous 3 months. His appetite was poor and he had lost 20 pounds. Bowel movements had become irregular so that for the first time in his life he had had to take cathartics. During the past 3 or 4 years he had nocturia varying from three times nightly to every hour.

The patient had been in another hospital from Feb. 8, 1935, to March 28, 1935, supposedly for pneumonia. He was again a patient in that same hospital in August, 1935, at which time an enlarged left inguinal lymph node was removed and a diagnosis of Hodgkin's disease was made microscopically.

Physical Examination: On examination the patient did not appear very ill but was weak. The skin was pale and the sclerae yellowish. A firm, freely moveable mass 2 to 3 cm. in size was palpable in the left submaxillary region. In the left inguinal region an elongated firm mass was found. In the left femoral region was a larger mass about 8 cm. in diameter. It was irregular and felt like "matted" lymph nodes. There was an overlying healed scar from the previous biopsy incision. The liver and spleen were not palpable. The prostate was not enlarged but was hard and many pus cells were seen in the secretion.

Laboratory Data: The first blood examination showed 64 per cent hemoglobin, 3,480,000 red cells, and 4600 leukocytes, with a differential count of 35 per cent lymphocytes, 45 per cent neutrophiles, 10 per cent eosinophiles and 10 per cent basophiles. The blood Kahn test was negative. Three blood cultures were negative but a fourth showed a few colonies of *Streptococcus viridans*. Macroscopic agglutination tests for *B. typhosus*, *B. paratyphosus A* and *B*, *B. dysenteriae*, *B. enteritidis* and *B. melitensis* were negative. The sputum was repeatedly negative for acid-fast bacteria and a tuberculin skin test was negative.

Urine examinations showed albumin from a trace to +, and many pus cells. The specific gravity was always between 1.006 and 1.012. A phenolsulphonephthalein excretion test showed 75 per cent retention after 2 hours. A Congo red test showed 56 per cent of the dye retained in the blood after 1 hour. The blood urea nitrogen varied between 58.8 mg. and 64 mg. on several occasions. The stools on several occasions showed blood, and a proctoscopic examination revealed a small mucosal ulcer in the lower colon.

Course of Illness: The clinical diagnosis was Hodgkin's disease, secondary anemia and renal insufficiency. The patient developed a septic type of temperature with irregular peaks up to 104° F. Ascites appeared and it was thought that the abdominal lymph nodes were involved by the Hodgkin's disease. An abdominal paracentesis yielded nearly 6 liters of light yellow fluid with a specific gravity of 1.012. This contained few cells, and was negative on bacterial culture and guinea pig inoculation.

The patient received deep X-ray therapy to the mass in the neck on Sept. 12, 1935; to the left groin and femoral region on Sept. 12, 1935, and again on Oct. 15, 1935. These treatments caused complete regression of the enlarged superficial lymph nodes. Three weeks after admission a blood count showed 15,000 white cells, with a differential count of 6 per cent small lymphocytes, 2 per cent large lymphocytes, 4 per cent monocytes, 5 per cent eosinophilic and 83 per cent neutrophilic polymorphonuclear leukocytes. Liver extract was not successful in combating the severe anemia. The pulse was always rapid and varied from 80 to 128. The blood pressure was low, varying from 90/56 to 102/66. The patient gradually grew worse and died on Nov. 12, 1935, after having been in coma for 2 days.

Postmortem Examination

The body was that of an emaciated and cachectic male. There was a slight generalized icterus. The mucus membranes were pale. The abdomen was slightly protuberant and had a fluid wave. Slight pitting edema of the ankles and feet, and edema of the scrotum were present. No enlarged lymph nodes were palpable in the neck, axilla or groin. The skin of the lower part of the left groin and upper part of the thigh was pigmented a deep brown over an area measuring 15 by 15 cm., which was obviously the result of therapeutic irradiation. In this region also was a healed surgical scar 7 cm. long, the site of biopsy. Beneath the skin the tissues were slightly indurated but no masses were palpable and nothing resembling residual lymphogranulomatous or lymph node tissue was found on dissection. Several healing furuncles were present on the trunk.

The abdominal cavity contained about 3 liters of a clear, yellowish green fluid. The peritoneal surfaces were everywhere thickened and semiopaque. There were firm fibrous adhesions about the gallbladder. The liver was exceedingly small and was far above the costal margin. The mesenteric lymph nodes were not enlarged.

Lungs: At the apex of each lung were a few fibrous pleural adhesions. The left pleural cavity contained about 100 cc. of yellowish fluid. There were no enlarged lymph nodes in the thorax. The lungs showed grossly and microscopically a bilateral hypostatic bronchopneumonia and an acute bronchitis. In the right lower lobe was a subpleural, well encapsulated caseocalcareous tubercle 1 cm. in diameter, with several smaller satellite tubercles, all entirely inactive. There was no recognizable thymic tissue.

Heart: The emptied heart with 1 cm. of attached aorta weighed 240 gm. The decrease in size was uniform. The myocardium was pale and flabby. The right chambers were overdistended. There was no visible myocardial scarring or fatty change. The valves were normal for the age. There was a minimal amount of atherosclerosis in the coronary arteries and a moderate amount in the lower part of the aorta. No other vascular changes were noted except that the veins of the portal system were conspicuous and distended. The portal vein was 30 mm. in circumference after it was emptied.

Kidneys: The right kidney measured only 5.5 by 3.5 by 2 cm. The perirenal fat was adherent to the surface by fibrous adhesions. The kidney consisted mostly of a large renal pelvis whose walls were greatly thickened. Only a thin shell of what suggested kidney tissue persisted at the periphery. The kidney remnant weighed only 15 gm. Much of this was pelvic fat.

The left kidney weighed only 90 gm. The perirenal fat was also excessively adherent. The surface was pitted by deep, irregular fibrous scars to which the capsule was firmly adherent. On cut surface, fairly normal cortex appeared between the retracted scars but over them there was nothing suggesting cortex. The renal pelvis was greatly dilated and its mucous membrane was greatly thickened and opaque.

Other Organs: The right ureter was greatly dilated and the left moderately so. The walls of each were about twice the usual thickness and were opaque. There was no obstruction in either ureter. The urinary bladder was thick walled and the trabeculation was conspicuous. The mucous membrane was everywhere opaque, and was hyperemic over the trigone. There was one large and numerous small diverticulums. The prostatic urethra was not obstructed. The membranous and penile parts of the urethra were unfortunately not examined and the nature of the obstructing lesion hence not

determined. The testes were grossly normal but microscopically there was an absence of spermatogenesis. They had possibly been irradiated when the femoral lymph nodes were treated. The gall-bladder was small, shrunken, thick walled and viscous with fibrous adhesions from the fundus to the surrounding viscera. It contained normal appearing thick bile. The extrahepatic bile ducts showed no changes. The central nervous system was not examined. The muscular system showed wasting and the muscles that were examined were pale. There were no recognizable skeletal changes. The bone marrow from the lower lumbar vertebra was a pale pinkish gray. The pancreas, adrenals and seminal vesicles showed no important changes. The gastro-intestinal tract showed only postmortem changes except in the rectum where the hemorrhoidal veins were dilated.

At autopsy the gross evidence of lymphogranulomatosis was confined to the liver, spleen and lymph nodes. Microscopically foci were also found in the bone marrow. Of the lymph nodes only the left iliac and left aortic were involved postmortem, although during life, as previously mentioned, other groups had been enlarged.

Lymph Nodes: Surrounding the left external iliac artery was a chain of firm and greatly enlarged but flattened lymph nodes. Similar nodes lined the pelvis around the internal iliac artery. The largest node measured 5.5 by 1.5 by 3 cm., and the largest fused mass of nodes measured 10 by 3 by 2 cm. On the surface made by cutting, the lymph nodes were fibrotic and pale yellowish to grayish pink. Along the left common iliac artery the enlarged lymph nodes formed a continuous chain. Extending upward the nodes along the left side of the aorta to the level of the left renal artery were enlarged, the largest measuring 1.5 cm.

Spleen: The spleen weighed 205 gm. and was firmer than usual. Although the capsule was thickened it was slightly wrinkled except for certain areas where indistinct projecting masses kept it smooth. The largest of these bulging areas was 3 cm. in diameter and projected about 8 mm. above the surrounding surface. About a dozen smaller masses, the largest of which was 8 mm. in diameter, were scattered over the surface. They were a darker reddish brown than the surrounding spleen tissue. On cut surface the spleen was reddish brown with obscure normal markings. The nodules seen on the surface were not sharply demarcated, but their extreme centers were a

paler grayish red than the splenic tissue which surrounded them. A few, firm, yellowish bodies, 1–2 mm. in size, apparently healed miliary tubercles, were also seen on the cut surface.

Liver: The liver was small, measuring 19 by 12 by 8 cm., and weighed 855 gm. The specific gravity seemed to be increased and the organ was firm. The capsule was uniformly slightly thickened. The right lobe was decreased in size proportionately more than the left. The anterior margin was rounded. The color was a pale brownish gray. The surface was uniformly finely nodular. The organ cut with increased resistance. The surfaces made by cutting were firm, almost hard, and did not bulge. The lobules varied in size but were on the whole smaller than normal. The centers were brownish red while at the periphery the tissue was grayish. There was no fat on scraping and no remarkable gross increase in connective tissue. These changes were uniform throughout all lobes of the liver.

Anatomical Diagnoses: Fibrous malignant lymphogranulomatous (Hodgkin's disease) infiltration of the spleen, liver, bone marrow and left iliac and aortic lymph nodes; malignant lymphogranulomatous cirrhosis of the liver; passive congestion of the portal system; chronic passive congestion of the spleen; ascites; fibrous thickening of the peritoneum; generalized icterus; generalized anemia; healed bilateral suppurative nephritis; left hydro-ureter and hydronephrosis; marked cystitis; multiple diverticulums of the urinary bladder; bilateral hypostatic bronchopneumonia; acute tracheitis and bronchitis; left hydrothorax; bilateral focal fibrous pleuritis; subpleural calcified tubercles; parenchymatous degeneration of the myocardium; atrophy of the heart, thyroid, pancreas and adrenals; dependent edema; fibrous cholecystitis and pericholecystitis.

Specific Microscopic Features

Lymph Nodes: Sections of numerous lymph nodes from the pelvis around the left external, internal and common iliac arteries, and of the left aortic nodes, showed essentially the same changes. The nodes were enlarged and the normal architecture was completely absent. They were composed almost entirely of fibrous connective tissue, but there were small scattered areas in which the cellular characteristics of Hodgkin's disease were still present. Such areas showed a diffuse increase in reticulum cells. These cells varied greatly in size, the larger ones grading over imperceptibly into

mononuclear giant cells. Some of these reticulum cells had large nuclei in which enlarged nucleoli were often present. Intermingling with these reticulum cells were many lymphocytes, numerous eosinophilic leukocytes and a few neutrophiles. Fibroblasts and young connective tissue cells were scattered throughout these areas and here and there were large mononucleated and multinucleated giant cells of the Sternberg-Reed type. Participation of the vascular endothelium was minor. Small scattered areas of necrosis were present. The fibroblastic reaction was the outstanding feature, and it is to be borne in mind that this was spontaneous, these lymph nodes never having been irradiated. Lymph nodes in the left femoral, cervical and axillary regions were not recognizable and consequently sections were not made. The thoracic lymph nodes contained no lymphogranulomatous tissue.

Spleen: Aside from a diffuse reticulum cell hyperplasia, a slight diffuse fibrosis, absent malpighian bodies and small foci of hematopoiesis in the sinusoids, the spleen showed poorly outlined nodules showing Hodgkin's lymphogranuloma. They consisted of mixtures of cells in which reticulum cells predominated but Sternberg-Reed cells, eosinophiles, lymphocytes and fibroblasts were also present. These areas were not fibrotic.

Bone Marrow: Marrow from the rib, femur and lower lumbar vertebra showed active hematopoiesis. The vertebral marrow, in addition, showed microscopic foci of Hodgkin's lymphogranulomatous tissue resembling those seen elsewhere.

Liver: The liver lobules in general showed a decrease in size and a few seem to have entirely disappeared, although there was no evidence of active destruction of liver cells. There was slight evidence of regeneration. The main change was a monolobular periportal cirrhosis. Many portal triads were surrounded by a mature, relalively acellular connective tissue. In other places the connective tissue was less mature and caught in the collagen were eosinophiles, large mononuclear cells and lymphocytes. In some periportal areas these cells were numerous and intermingled with them was an occasional Sternberg-Reed type of giant cell. In a few places richly cellular lymphogranulomatous tissue unaccompanied by much fibrous connective tissue enclosed portal triads. The lymphogranulomatous tissue resembled that seen in the lymph nodes. Nowhere did it form nodules visible to the naked eye. Studying the micro-

scopic sections it was easy to find periportal foci gradually grading from those extremely cellular, apparently recently formed, to others partly sclerotic, and from there to still others entirely sclerotic and consequently unrecognizable with certainty as lymphogranulomatous in origin. The liver showed a minute amount of fatty change and no evidence of active inflammation. The bile ducts were relatively unchanged.

Discussion

The most interesting feature of this case is the possible pathogenesis of the cirrhotic liver. The author's interpretation is that there was an exceptionally widespread distribution of malignant lymphogranulomatous tissue throughout the liver along the portal areas. Just as in the lymph nodes the diseased tissue underwent an unusually extensive spontaneous fibrosis, so in the liver there was cicatrization. Because of the exceptionally widespread distribution in the liver and its localization in the periportal areas, this fibrosis produced the cirrhotic liver with its clinical picture of portal obstruction. Although the speed of the process varies greatly in different cases, the natural course of lymphogranulomatous tissue leads to fibrosis. Irradiation accelerates this process.

The question can legitimately be raised as to whether the scar tissue in the liver represents the fibrous endstage of malignant lymphogranulomatous tissue or whether it represents a coexisting but independent type of cirrhosis of the liver. The histopathological picture is in favor of the former. Nodular periportal accumulations of cells with the diagnostic characteristics of Hodgkin's disease are undoubtedly present. Other areas showing increased fibrosis but still recognizable as malignant lymphogranulomatous in nature are also present. Finally a point is reached where the periportal tissue is extremely fibrous and in it are seen cells that are still suggestive but not diagnostic of Hodgkin's disease. The morphological evidence points to its origin from lymphogranulomatous tissue.

What other type of cirrhosis of the liver could be coexistent in this case? The only type that suggests itself seriously is atrophic cirrhosis. But there is strong evidence against this idea. In the first place it was not possible to demonstrate the specific "alcoholic hyalin" described by Mallory [3] in microscopic sections. Secondly, the small size of the liver, while not conclusive, speaks against its being due to atrophic cirrhosis. In Mallory's series of cases [4] the

smallest livers classified as atrophic cirrhosis weighed 950 gm. In a large series of cases studied at the University of Chicago the smallest livers classified as atrophic cirrhosis weighed about 920 gm. Smaller cirrhotic livers occurred in the group classified as "healed toxic necrosis," but here the pathological picture is different from that seen in the case under discussion. In the third place there are larger areas devoid of fibrosis than are usually seen in atrophic cirrhosis; and, in the fourth place, the gross appearance is not typical of a hobnail liver. The uniformly finely nodular surface without bulging nodules of regenerated liver cells or retracting scars is not commonly seen in atrophic cirrhosis after the liver has become as small as the one here under consideration.

Although changes in the liver resembling those described in this case have undoubtedly been seen by others, the writer is aware of no description of such cases. Periportal lymphogranulomatous infiltration has been described but in the cases reported it had not reached the degree of cicatrization seen in this case. In the case that Symmers [2] described (Case VIII) there was a massive lymphogranulomatous infiltration in and about the portal areas so that a greatly enlarged liver was produced. Fibrous healing was minimal and there was no cirrhosis. Foulon's [5] Case I appears to have had less infiltration with Hodgkin's disease and no notable sclerosis in an enlarged liver. In Schmorl's [6] case the infiltrate was cellular and not scirrhous, so that he spoke of it as a peripylephlebitic lymphogranulomatosa. All of these cases could conceivably have led to an endstage such as that described by the writer if the fibrosing tendency had been greater. They can therefore be considered as earlier stages of this process.

Cicatrizing lymphogranulomatosis of the liver was reported by Weis and Fraenkel.[7] In their case the fibrosing of a few large lymphogranulomatous nodules produced coarse deep scars which divided the liver into large lobules. The final picture resembled that seen in syphilitic hepar lobatum. The 2nd case of Goia,[8] in his discussion of the liver changes in malignant lymphogranuloma, resembles that of Weis and Fraenkel.

Unfortunately the case reported here offers no information as to the etiology of Hodgkin's disease, and in regard to the constantly recurring question as to whether it is neoplastic or infectious in nature. Cirrhosis of the liver may be produced by neoplastic metastases and also by chronic infectious processes. Infectious biliary

cirrhosis is an example of the latter. Bacaloglu *et al.*,[9] have recently described examples of cirrhosis produced by neoplasms.

Summary and Conclusions

The case of a white male, aged 55 years, who for about 2 years had had painless enlargement of superficial lymph nodes is presented. Biopsy of an inguinal node about 3 months before death revealed the histological picture of malignant lymphogranuloma (Hodgkin's disease). Following X-ray therapy the enlarged superficial lymph nodes disappeared, showing the characteristic therapeutic response. The patient, however, developed a portal obstruction with jaundice, ascites, rectal bleeding and anemia. Postmortem examination revealed lymphogranulomatous involvement only of the lymph nodes in the left side of the pelvis about the iliac vessels and along the left side of the abdominal aorta. Microscopically the enlarged nodes were extremely scirrhous, only small foci of lymphogranulomatous tissue persisting. This was a spontaneous fibrosis, these regions never having been irradiated. Lymphogranulomatous tissue was also present in the spleen and in the vertebral bodies.

The liver was small, firm and finely nodular, and weighed 855 gm. Microscopically it showed a monolobular cirrhosis with little fatty change, regeneration or active necrosis. About scattered periportal areas were cellular granulomatous foci with the diagnostic features of Hodgkin's lymphogranuloma. Other areas, while still typical of the same disease, showed increasing amounts of fibrosis, but other periportal foci considered to be analogous, but farther advanced, showed only fibrous connective tissue.

The author's interpretation is that just as in the lymph nodes there was an unusual degree of spontaneous fibrosis, so in the liver the unusually widespread periportal lymphogranulomatous infiltration underwent the same process. This resulted in a small cirrhotic liver which produced the clinical effects of portal obstruction and death.

Note: I am indebted to Dr. L. H. Sloan for permission to use the clinical record in this case. Experienced pathologists have studied the case and have agreed with the interpretation. My colleagues, Drs. H. Gideon Wells, P. R. Cannon, and E. M. Humphreys and Drs. J. P. Simonds, F. W. Stewart and F. D. Gunn are among those to whom my thanks are due.

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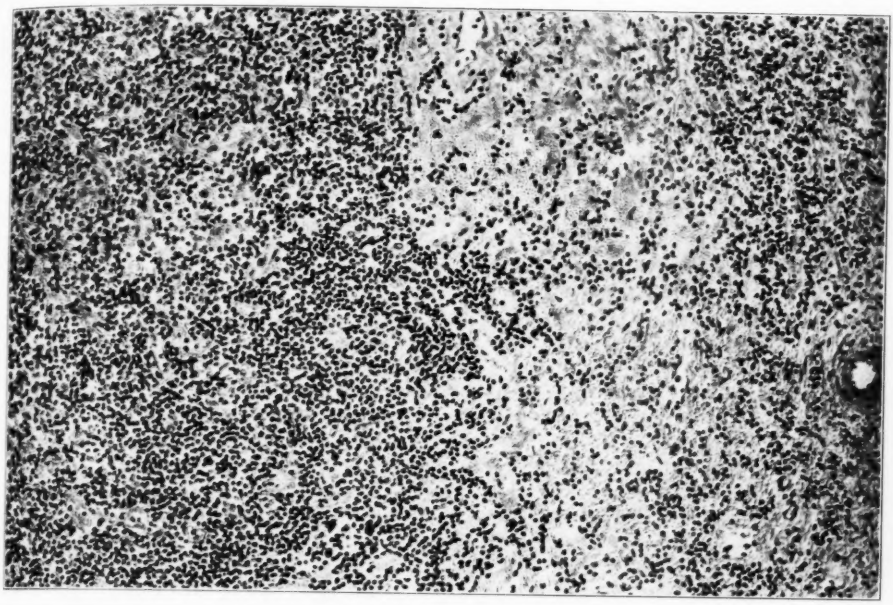
DESCRIPTION OF PLATES

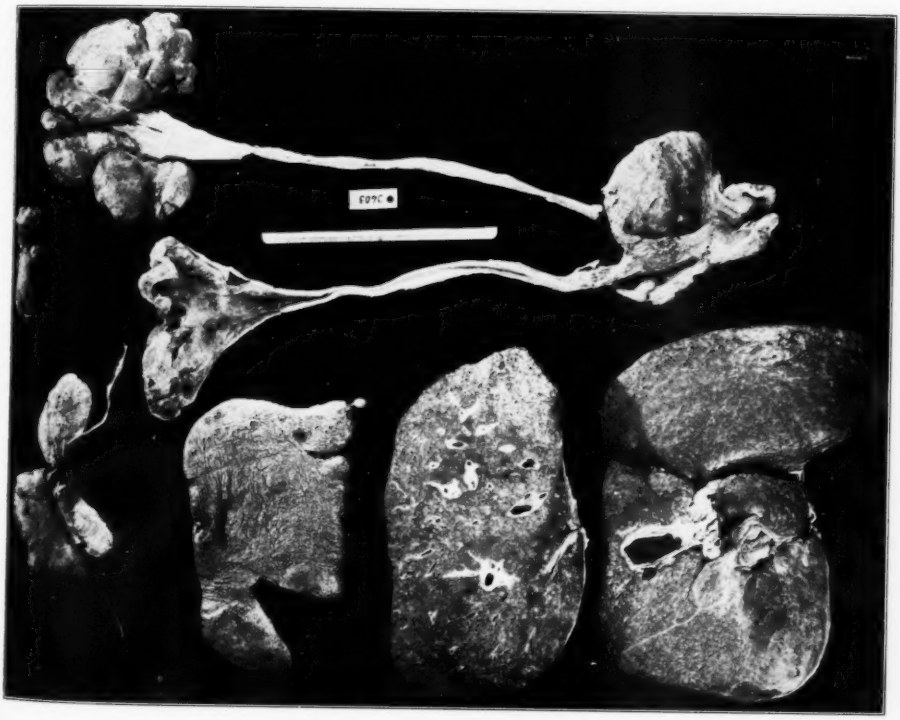
PLATE 15

FIG. 1. The photograph shows at the upper left the enlarged iliac lymph nodes. The probe passes through the external iliac artery. The group of smaller nodes is from the left side of the abdominal aorta. The enlarged spleen shows indefinite nodular elevations. Of the liver both a surface made by cutting and the inferior surface are shown. The decrease in size and the fine nodularity can be seen. Old bilateral kidney destruction and multiple small diverticulums of the urinary bladder are shown.

FIG. 2. Lymph node showing destruction of the normal architecture and infiltrating fibrosis. × 150.



2



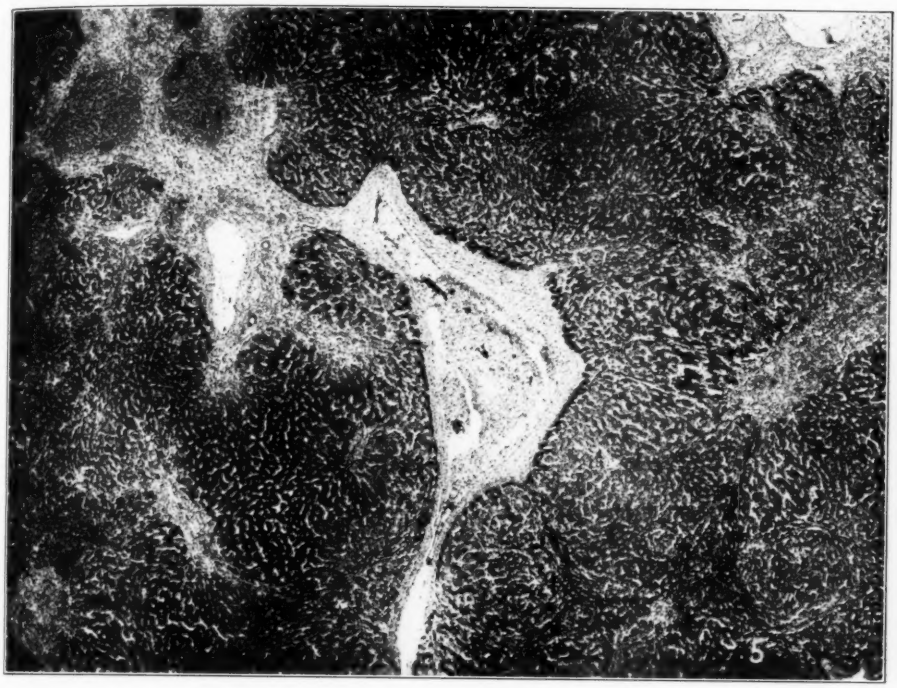
1

Steiner Lymphogranulomatous Cirrhosis of Liver

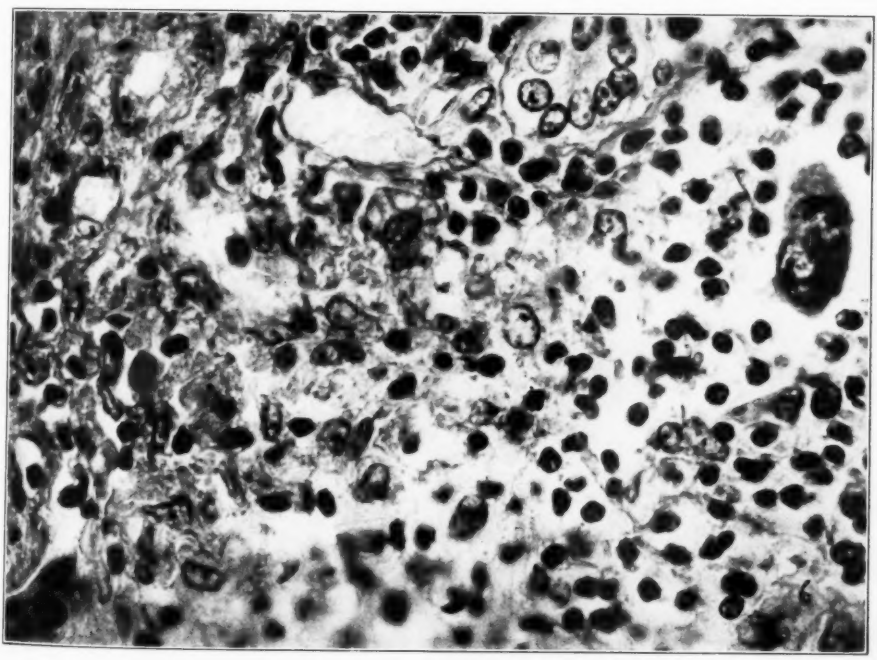
PLATE 16

FIG. 3. Section of liver showing three stages in the fibrotic process. At the extreme lower left and at the center at the right margin are cellular, periportal, lymphogranulomatous nodules. At the upper left are two partly fibrotic lymphogranulomatous foci. Just below them and at the upper right are completely fibrotic periportal areas. × 25.

FIG. 4. Higher power view of one nodule at the upper left of Figure 3 to illustrate the specific diagnostic features of Hodgkin's lymphogranuloma. × 650.



3



4

Steiner Lymphogranulomatous Cirrhosis of Liver

ACUTE BACTERIAL ENDOCARDITIS DUE TO PSEUDOMONAS ÆRUGINOSA (B. PYOCYANEUS)*

Report of a Case

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Reports of septicemia due to *B. pyocyaneus* occur not uncommonly in the literature, but cases of endocarditis due to this organism constitute a definite rarity. We have been able to find only 1 in the English journals. Four, however, have been reported in the German literature.

Blum [1] in 1899 recorded the case of a 2½ months old male infant suffering from congenital syphilis with rhinitis, rhagades and a skin eruption. Autopsy revealed endocarditis of the mitral valve, the vegetation containing many Gram-negative bacilli. *B. pyocyaneus* was isolated from the heart's blood. A culture of this organism, injected into a rabbit, after mechanical laceration of the aortic valve, produced an endocarditis.

De la Camp [2] in 1903 published a case of chronic pyocyaneus Septicemia, with polyarthritis and hemorrhagic diathesis. At autopsy bacterial endocarditis of the mitral valve was found, from which *B. pyocyaneus* was obtained in pure culture.

Rolly [3] in 1906 reported a case of a female, 28 years of age, who had a typhoid-like septicemia lasting 11 days. She also had some meningeal symptoms. Blood and spinal fluid cultures showed pure *B. pyocyaneus*. Postmortem examination revealed bacterial endocarditis implanted on an old rheumatic mitral valve, meningitis and metastatic abscesses of spleen and kidneys. *B. pyocyaneus* was demonstrated in sections of the valve and in the walls of arteries.

Among the cases of endocarditis which Thayer [4] analyzed in 1926 was that of a female, 42 years of age, who had had diarrhea for 4 weeks with vomiting, anorexia and asthenia. She died 7 days after admission to the hospital, having had a subnormal temperature the

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entire time except for one rise to 99.4° F. At autopsy a few small vegetations on the posterior leaflet of the mitral valve, with a large one on the anterior leaflet, were found. Other lesions included chronic pelvic cellulitis, ulceration of the small and large intestine with perforation and peritonitis, rectovaginal fistula, old tuberculosis of lungs, bronchiectasis, fibrinopurulent pleurisy, hydronephrosis with amyloid kidneys and carcinoma of the stomach. Cultures from the mitral vegetation, peritoneum and intestinal ulcers yielded pure *B. pyocyaneus*. Short thick and long slender rods were seen in the sections of the mitral valve.

Büngeler [5] in 1927 published a case of a 65 year old male who 7 years before death had developed endocarditis following erysipelas, and who showed physical signs of mitral insufficiency. Because of a "nervous disease" he was given repeated intravenous injections of a preparation of saprophytic bacteria called "saprovitan." This was subsequently proved to contain *B. pyocyaneus*. He became febrile and died after a septicemia lasting 16 days. Multiple verrucae were found on the mitral valve leaflets, with a perforation 1 cm. in diameter, about which were larger thrombotic masses. The kidneys contained miliary abscesses. Cultures from the spleen yielded *B. proteus*, *B. pyocyaneus* and short chains of a hemolytic Gram-positive cocci not pathogenic for mice. No histological or bacterial study was made of the vegetations on the mitral valve. To ascribe the endocarditis to *B. pyocyaneus* is to draw a conclusion that seems to us quite untenable.

Report of Case

Clinical History: R. B., a 71 year old white male, was admitted to the emergency room of Vanderbilt Clinic complaining of inability to void for 3 days. He had been catheterized three times by his family physician within the 3 days prior to admission, the last catheterization having been performed 15 hours prior to entry to the hospital. His first urinary symptoms were noticed 18 months previously when he developed acute retention, which recurred about every 6 months, necessitating catheterization in each instance. The only other urinary symptoms were nocturia twice, slow stream, and occasional dysuria for 18 months. Systemic, past and family histories were irrelevant.

Physical Examination: This revealed a well developed and well nourished, elderly white male. The temperature was 99° F., pulse 90 and respiration 20. Eyes, ears, nose and throat normal; heart sounds distant; blood pressure 110/80. Lungs clear. Bladder two-thirds of way to umbilicus. Prostate symmetrically enlarged, firm, freely movable and non-tender. Extremities and reflexes normal.

Laboratory Data: Blood urea on admission was 21.1 mg., blood sugar 105 mg. The hemoglobin was 75 per cent, red blood corpuscles 4,190,000, white blood

corpuscles 7050, polymorphonuclears 67 per cent, lymphocytes 28 per cent, eosinophiles 3 per cent, and mononuclears 2 per cent. The blood Wassermann was negative. The urine was bloody.

Cystoscopy was performed on the day of admission. The bladder contained 120 cc. of residual urine, was definitely trabeculated, and a number of small diverticulum openings were seen. There was increased intravesical intrusion of all lobes of the prostate.

A bilateral vasectomy was performed under local novocaine anesthesia, an indwelling catheter inserted the following day, and daily bladder irrigations with 1:5000 silver nitrate instituted.

X-rays of the chest showed evidence of an old pleurisy at the right base. X-rays of the genito-urinary tract were essentially negative. A cystogram with sodium iodide showed multiple diverticulums of the urinary bladder.

Course of Illness: The patient was given urotropin and acid sodium phosphate, 0.125 gm. of each daily, fluids were forced to at least 3000 cc. daily, and bladder irrigations with 1:5000 silver nitrate were given daily for 13 days. The blood urea at that time was 16.1 mg.

Fourteen days after admission a suprapubic prostatectomy was performed under gas and oxygen ether anesthesia, and a large, smooth, three-lobed prostate weighing 87 gm. was removed. The pathological report was fibroadenoma of prostate, focal suppurative prostatitis, and abscesses of prostate. Subsequently Gram-negative bacilli were found in these sections clustered around remnants of corpora amylacea in the abscesses. No organisms were seen in leukocytes. The postoperative course was uneventful until the 7th postoperative day when the patient's temperature suddenly rose to 103.4° F., and continued between normal and 105° F.

Physical examination failed to reveal the cause of the temperature and the patient had no complaints until the 19th postoperative day when he felt quite lethargic and developed a chill. A check of the blood count showed a hemoglobin of 55 per cent, red blood corpuscles 3,320,000, white blood corpuscles 9350, polymorphonuclears 80 per cent, lymphocytes 14 per cent, eosinophiles 3 per cent and mononuclears 3 per cent. A blood culture showed pure *B. pyocyaneus* and a blood transfusion of 500 cc. was given.

Five repeated blood cultures during the following weeks were all positive for *B. pyocyaneus*. In spite of repeated blood transfusions and continuous infusions of saline and 5 per cent glucose, the patient died on the 27th postoperative day.

Autopsy Report *

The body was that of a well developed but considerably emaciated male. A fistula connected the skin of the pubic region with the bladder, but was free of gross infection. Several petechiae were present in the right conjunctiva. The left pleural cavity contained approximately 200 cc. of slightly turbid yellow fluid; the right was obliterated by fibrous adhesions.

Heart: The heart weighed 500 gm. and appeared enlarged. A few small hemorrhages were present around the base of the great

* No. 11,919.

vessels. The tricuspid, pulmonary and mitral valves appeared normal. On the ventricular surface of the right posterior leaflet of the aortic valve was a finely lobulated, yellowish white shining mass approximately 0.75 cm. in diameter. It was quite firmly attached to the cusp and a thin strip of the same material was present on the aortic surface of the same leaflet, giving the impression that the process had extended through the valve.

Aorta: Just above the anterior sinus of Valsalva was a granular mass of calcium salts 0.5 cm. in its greatest diameter projecting from the surface of the intima. A similar deposit was found 1.5 cm. above the junction of the anterior and right posterior cusps. This deposit was 2 cm. long, longitudinally disposed, and attached to its center was a bit of thrombus. The rest of the aorta showed a fairly advanced arteriosclerosis.

Lungs: An early lobular pneumonia and bilateral obsolete tuberculosis were present.

Spleen: The weight of the spleen was 100 gm. and it was extremely soft.

Liver: The liver weighed 2140 gm., but was otherwise normal on gross appearance.

Kidneys: Several yellow infarcts were present.

Prostatic Bed: This was lined by necrotic greenish yellow material and presented a multiloculated appearance. The remnants of the prostate formed the walls of this cavity. The bladder was contracted.

Pancreas, Adrenals, Testes and Alimentary Tract: Apparently normal.

Brain and Cord: Not removed.

Microscopic Examination

Aortic Valve: Necrosis was present beneath the vegetation and there was infiltration with many polymorphonuclear leukocytes. The vegetation consisted of a mass of granular, pink staining material in which were many colonies of bacteria and a few leukocytes. A Gram stain revealed numbers of Gram-negative bacilli in the margin of the valve beneath the vegetation. The methylene blue stain brought out the bacilli more clearly.

Aorta: Section from the calcified area above the aortic valve, on which thrombus was present, showed a thickened and raised intima.

In the space beneath this area were masses of calcium and small numbers of polymorphonuclear leukocytes and red blood cells. The smooth muscle of the media was depleted beneath the plaque, the vasa vasorum were dilated and congested, and large numbers of polymorphonuclear leukocytes infiltrated the crevices between the elastic tissue and the muscle fibers around these vessels. The adventitia was normal. A methylene blue stain showed many groups of small bacilli in the crevices of the intima. No organisms were seen in leukocytes.

Liver: Focal necroses infiltrated with polymorphonuclear leukocytes occurred in the midzonal regions.

Kidneys: In many places the cells of the tubules were necrotic and the surrounding tissues infiltrated with polymorphonuclear leukocytes. A branch of the renal artery was filled with thrombus and its wall was infiltrated with polymorphonuclear leukocytes.

Prostate: Some hyperplastic glandular tissue was left. A few foci of acute inflammation with infiltration of polymorphonuclear leukocytes were found, as well as a thrombosed vein undergoing organization. No organisms were found in preparations stained with the Gram or methylene blue stains.

Anatomical Diagnoses: Benign hypertrophy of prostate (operation: prostatectomy), acute suppurative prostatitis; acute bacterial endocarditis of aortic valve due to *B. pyocyaneus*; bacteremia (*B. pyocyaneus*); acute aortitis; infarcts of kidneys; lobular pneumonia, confluent; hydrothorax, left; hydropericardium; central necroses of liver; pulmonary tuberculosis, bilateral, obsolete; fibrous pleural adhesions, bilateral; generalized arteriosclerosis; and medial calcification of aorta.

Discussion

Most cases of *B. pyocyaneus* septicemia have occurred in children. Usually the umbilicus (in infants), the skin of the anogenital region, and the lower intestinal tract have been implicated as the portals of entry. We think it a reasonable assumption in the case here reported that the prostate was the focus from which the bacteria were distributed, since Gram-negative bacilli were demonstrated in the surgical specimen.

Many authors have called attention to a hemorrhagic diathesis which is evidenced in these cases by cutaneous vesicles filled with

bloody fluid and by bloody diarrhea. These symptoms, combined with prostration, have sometimes produced a typhoid-like picture. No such lesions were observed in our case.

One of the most interesting features of pyocyaneus infection is the affinity of the organism for the walls of arteries. Rolly [3] demonstrated them in the arteries of his case. Fraenkel [6] described an acute arteritis in the vessels supplying the area of inflammation, with the cellular reaction usually occurring in the media or adventitia. The case we have reported also showed acute arteritic lesions in the aorta and in branches of the renal artery. Bacilli were demonstrated in the aorta. In spite of the fact that an intense polymorphonuclear reaction occurred in both the aorta and the prostate, the bacilli could never be found in the leukocytes but were always clustered around fragments of necrotic débris.

Summary

1. A case of generalized infection due to *Pseudomonas æruginosa*, and associated with bacterial endocarditis, is reported.

2. The origin of the infection was found in the hypertrophied prostate gland, which contained suppurative foci and Gram-negative bacilli.

3. A distinctive pathological feature noted in several previously reported cases is acute inflammation of the aorta and renal arteries. Bacilli were found in great numbers in these lesions.

4. The few previously reported cases of *Pseudomonas æruginosa* endocarditis are briefly reviewed.

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DESCRIPTION OF PLATE

PLATE 17

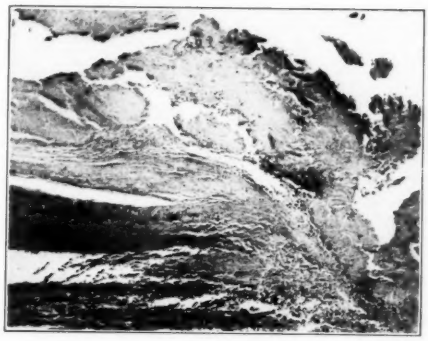
FIG. 1. Vegetation on aortic valve with infiltration of polymorphonuclear leukocytes. Hematoxylin and eosin stain. × 65.4.

FIG. 2. Bacilli in vegetation. Methylene blue stain. × 763.6.

FIG. 3. Acute aortitis. Hematoxylin and eosin stain. × 124.

FIG. 4. Bacilli in crevices of aorta. Methylene blue stain. × 763.6.

FIG. 5. Bacilli around fragmented corpus amylaceum in abscess of prostate. Methylene blue stain. × 763.6.



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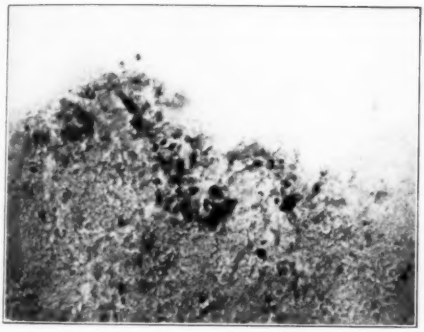

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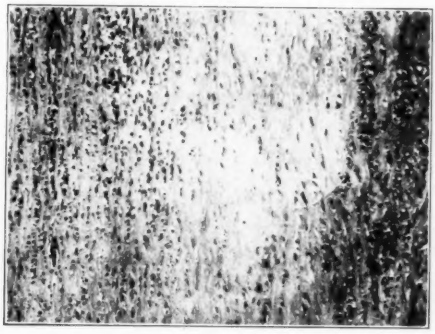

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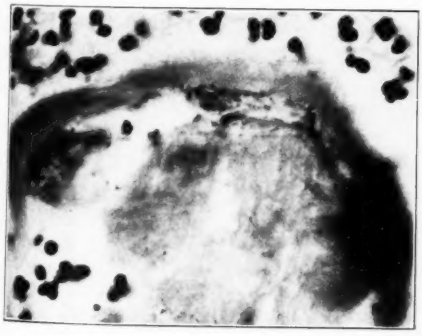

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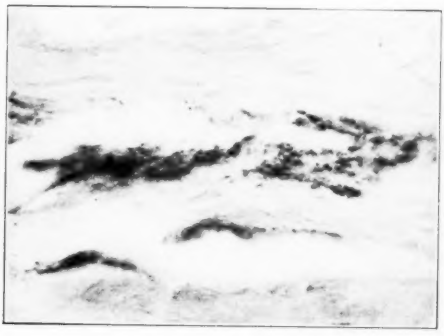

5

Fish, Hand and Keim

Endocarditis due to *Pseudomonas Æruginosa*

PRIMARY FIBROBLASTOMA OF THE BRAIN *

Report of a Case

A. B. Baker, M.D., and John M. Adams, M.D.

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Cerebral neoplasms composed almost exclusively of fibroblastic elements are extremely uncommon. Although the exact origin of these tumors is unknown, it seems permissible to call them fibroblastomas because their structure differs strikingly from that of the much more common tumors of neuro-ectodermal origin, and because of their resemblance to fibroblastomas elsewhere. Up to the present time only 4 such tumors have been reported in the literature. In 1929 Bailey [1] reported 2 cases. His 1st case was one studied by Dr. F. B. Mallory. This was a semiopaque, somewhat cartilaginous mass found in the right temporal lobe of a 42 year old female. It was adherent to the dura. Histologically the tumor was a fairly typical fibrosarcoma and was composed of spindle shaped cells. Between these cells were numerous reticulin and collagen fibers. Mitotic figures were numerous. Bailey's 2nd case was an operative specimen removed from the inner wall of the right lateral ventricle of a 19 year old male. This tumor was reddish in appearance and was so soft that it was removed by suction. The tumor was composed of streams of spindle shaped cells running in various directions. The cells had a delicate cytoplasm and an oval or elongated nucleus containing dust-like chromatin material. Mitotic figures were numerous. The collagen was most abundant in the degenerated areas of the tumor, while delicate reticulin and fibroglia fibrils made up the bulk of the remaining intercellular substance. Vascular sinuses were quite numerous.

In 1930 Mallory [2] reported a case of a 33 year old male in whom a tumor nodule measuring 5 cm. in diameter was found at autopsy in the right frontal lobe. Grossly this newgrowth was of unusual firmness and whiteness. Histologically it was described as being well differentiated, rather slowly growing, and a typical fibrosarcoma. This patient had also two large adrenal tumors that were apparently not related to the cerebral lesion.

* Received for publication July 6, 1936.

Alpers, Yaskin and Grant[3] in 1932 reported the removal of a tumor the "size of a walnut" from the right frontotemporal region of a 52 year old male. It was encapsulated, firm, white and fibrous. Histologically the tumor cells were loosely packed and in some regions had a definite myxomatous appearance. There was a rich intercellular substance composed chiefly of fibrous tissue and fibrils that were apparently fibroglia. Blood vessels were numerous and areas of degeneration were present. Neuroglial cells were found only at the edge of the tumor, but not within it. The authors described numerous tumor cells closely related to the walls of the vessels. These cells were in a stage of proliferation and were assumed to be "centers of growth" of the tumor.

Because of the rarity of this type of cerebral neoplasm and because of the interesting problems in histogenesis involved, a report of a further case seems permissible.

Report of Case*

Clinical History: The patient, a white female aged 10 years, was first seen at the University of Minnesota Hospital on Feb. 17, 1936, at which time she complained of headache, vomiting, visual disturbances and weakness of the left side of the face, left arm and left leg.

The birth history was uneventful: head presentation, spontaneous delivery, and a birth weight of 8 pounds. Physical development was quite normal. She had had the usual childhood diseases but no diphtheria, poliomyelitis, meningitis or mumps. The family history was negative, her father and mother both being well. There was no history of nervous disorders in the family. Two brothers and 3 sisters are living and well. There was no history of tuberculosis or contact with the disease.

The present illness dated from the first week in December, 1935, at which time she fell from a chair, striking the right occipital region. She did not lose consciousness. On careful questioning the patient herself stated that she had had a few headaches a short time prior to the accident. The headaches became almost constant afterward. Vomiting began about Jan. 1, 1936, occurred every 3 to 5 days, the interval becoming shorter until it was a daily episode. The vomiting was projectile in character.

Three weeks before admission (about Jan. 28, 1936) she awoke at night, cried out, and had a severe attack of vomiting, following which she noticed weakness and numbness of the left arm and hand. The weakness of the left side of the face was present after that time.

These symptoms progressed until admission to the hospital, at which time the patient complained of constant severe headache, daily attacks of vomiting and great weakness of the left side of the body. It was almost impossible for her to walk.

Physical Examination: The patient presented a bright, intelligent and cooperative girl of 10 years, well developed but slightly undernourished. The

*Hospital No. 646071.

muscles of the left side of the face were relaxed, the right eyelid closed tighter than the left and the facial muscles retracted toward the right on showing the teeth. The pupils reacted to light. The eyegrounds showed a high degree of choking, 5–6 diopters with engorgement of the veins, a few, small, flame shaped hemorrhages and a partially developed macular star, suggesting that the choke was of considerable duration.

The chest was symmetrical, the lung fields clear, the heart not enlarged to percussion and the sounds clear. There were no murmurs. Abdominal examination was negative. No lymphadenopathy was present.

The right eye could not be moved upward or laterally. Diplopia was present. The tongue protruded in the midline. There was marked weakness of the lower left facial musculature. The abdominal reflexes were decreased on the left. The Babinski reflex was positive on the left. The deep reflexes could not be obtained. The stereognostic sense and sensation were normal. There was partial motor weakness of the left arm and leg.

The impression on admission was that the patient had a neoplasm in the midbrain, in the area of the mesencephalon on the right, involving the third and fourth cranial nerves, with pyramidal tract involvement before crossing.

Laboratory Data: There were no significant routine laboratory findings.

X-ray examination of the skull revealed evidence of intracranial pressure with irregular erosion of the inner table of the skull visible as multiple finger prints. There was beginning separation of the sutures. The sella and clinoid processes were not involved.

Course of Illness: The patient was given 75 cc. of 30 per cent sucrose intravenously, and on Feb. 19, 1936, a subtemporal decompression was performed inferior and posterior to the motor area on the right side. The amount of bone removed measured about 4 by 4 cm. There was considerable increased pressure encountered and extremely large blood vessels were present on the surface of the brain after cutting the dura. An attempt to enter the anterior horn of the ventricle was unsuccessful, considerable resistance being met with in that area. The impression of the surgeon was that this portion of the ventricle was infiltrated with tumor.

Following operation the temperature rose to 100.5° F., the pulse averaged between 80 and 100, going up to 130 on one occasion; the respirations averaged 15 to 20 per minute; and the blood pressure averaged 115/80. On Feb. 20, 1936, 70 cc. of 15 per cent sucrose was given intravenously. The patient's course for the next 2 weeks was essentially uneventful. A course of deep X-ray was begun on February 26th. She was given six treatments extending over 12 days, consisting of 140 per cent skin erythema dose to each lateral skull field. On March 13, 1936, 24 days following operation, the temperature rose abruptly to 105° F., the pulse to 140 per minute. She was restless and complained of severe headache over both eyes. The brain gradually herniated from the wound, extending finally about 3 cm. above the skin margin. Signs of meningitis were evident. The temperature remained elevated, averaging 103° F., with pulse about 130 per minute. On March 22, 1936, the temperature rose to 106° F., the pulse to 180, and the respiration was 60. The patient died the same day.

Autopsy Report

The autopsy was limited to an examination of the head. The entire surface of the brain was covered with a yellowish purulent

exudate which tended to accumulate within the large cisternae. There was a slight herniation of the brain tissue in the region of the decompression in the right middle frontal gyrus.

In the posterior portion of the right middle and inferior frontal convolutions there was a brownish discolored area measuring 5 by 4 cm., covered by a thin layer of brain tissue that apparently separated this discolored mass from the surface. Palpation over this region revealed a definite firmness and resistance to pressure. Separation of the cerebral hemispheres revealed a slight displacement toward the left of the medial border of the right cerebral hemisphere above the corpus callosum.

Coronal sections through the posterior third of the right frontal lobe of the brain exposed a well circumscribed, sharply demarcated brain tumor measuring 5 by 5 by 5 cm. (Fig. 1). The tumor did not appear to be invasive but merely replaced, probably by compression, portions of the cortex and white substance. Its lateral surface extended almost to the surface of the brain, being separated from the leptomeninges only by a thin layer of brain tissue. The mass itself was extremely firm, well outlined, but not encapsulated (Fig. 1). The cut surface was white, semiopaque, and almost gritty in appearance. There were no areas of degeneration, softening or obvious gross hemorrhage, although a few irregular reddish streaks were scattered throughout, apparently representing blood vessels or small hemorrhages within the tumor tissue. The tumor mass was entirely intracerebral and was not connected at any point with the meninges.

Microscopic Examination

Histologically the tumor presents a fairly uniform appearance. It consists of numerous fine and coarse strands of intertwining collagenous fibers that extend in various directions and present a fairly irregular architecture (Figs. 2 and 3). A moderate number of cells are interspersed among these strands of collagen (Fig. 2). The fibrous tissue composes the bulk of the intercellular substance and stains readily with the azocarmine stain. In some areas these intercellular fibers fuse to form dense, homogeneous wavy bundles of tissue that contain only an occasional cell nucleus and assume quite frequently a hyaline-like appearance. A plaque-like thickening of the tissue occurs in certain parts of these heavy fibrous bands.

These plaques stain more deeply than the surrounding connective tissue, probably because of its greater density. Only an occasional typical fibroblast is detected within the well defined plaques. In some of the relatively acellular regions the strands of collagen remain thin but intertwine with one another to give the effect of a reticular structure. No necrotic areas are apparent.

The tumor cells are irregular in outline. Some are round or oval in shape, although the majority are somewhat elongated and are composed of a small amount of cytoplasm surrounding a fairly irregular nucleus. These nuclei are large, slightly elongated, and contain a heavy, well demarcated nuclear membrane. Their chromatin is finely granular and although it is usually scattered throughout the nucleus, it occasionally assumes a peripheral distribution, being limited to the inner surface of the nuclear membrane. Frequently these granules merge to form larger chromatin clumps that resemble nucleoli in many instances. The cell body when visible extends from each end of the nucleus as bipolar cytoplasmic processes that merge with the surrounding intercellular substance. The cell cytoplasm stains very lightly with eosin and contains many fine granules.

In some areas the cells assume a definite stellate contour with numerous fine processes radiating out from the cell body. The intercellular substance in these regions is extremely fine and loose, causing the entire field to resemble myxomatous tissue quite closely.

Scattered among the fibroblasts are a few small cells with deeply staining round nuclei. These cells are probably microglia. No mitotic figures and no cells of glial origin can be made out within the tumor mass. The majority of the tumor cells present a structure quite typical of connective tissue cells and must be classed as fibroblasts and not as glial cells. With special stains numerous reticulin fibers can be seen scattered among the intercellular framework of the tumor (Fig. 3).

Blood vessels are numerous in all the sections studied. These vessels vary from endothelial lined cavities filled with blood to vessels composed of the typical layers ordinarily seen in cerebral arteries. The former are by far the more numerous and vary greatly in size and number. In those areas in which the vessels are most numerous, cells are also numerous. In no case, however, do these cells proliferate from or accumulate about the vessel wall to form

anything similar to the "centers of growth" described by Alpers, Yaskin and Grant [3] in their tumor.

Many hemorrhages are present within the tumor. Some of these are fairly well localized, while others are large and diffuse. Many of the hemorrhages consist merely of a fine film of erythrocytes scattered between the intercellular fibers, while others are composed of dense accumulations of red cells that completely mask the underlying structures. Most of the extravasations are not perivascular and appear to have no relation to the vessels. In some sections, however, a few hemorrhages that are distinctly perivascular in appearance are observed forming the so-called "ring" hemorrhages around the involved vessels.

In spite of the complete absence of a capsule the tumor is well demarcated from the surrounding brain tissue. The brain tissue adjacent to the neoplasm shows extensive glial and microglial reaction. The astrocytes reveal numerous proliferative changes and can be seen as large cells from which radiate numerous branching processes of variable length and thickness. Many of the astrocytes have become swollen to form giant glial cells. These cells frequently contain a finely granular cytoplasm and a considerably enlarged, irregular and often polymorphous nucleus. Many of these glial cells fuse to form large multinucleated cells. Although quite numerous in the adjacent brain tissue, these proliferating glial cells do not extend into the fibrous stroma of the tumor. Some of the astrocytes in the region of the tumor reveal degenerative changes consisting of fragmentation of the cell processes and pyknosis of the nuclei.

The microglia also reveal extensive alterations. As one passes from normal brain tissue toward the tissue adjacent to the tumor, all transitions of the microglia into rod cells and finally into fat granule cells can be observed. The latter cells are the most numerous and appear as large, irregular globular cells without cytoplasmic processes. The extensive proliferation and accumulation of these cells on the margin of the tumor have resulted in the migration of many of them into the adjacent tumor tissue. Many of these phagocytes are filled with hemosiderin which has been taken up from the region of a hemorrhage.

Discussion

We have called this tumor a primary fibroblastoma, even though the exact origin of these neoplasms is by no means certain. Since the

number of recorded cases of such tumors is so small, it is impossible to derive many definite facts concerning them from a review of these reports. It appears that these tumors may occur at any age period, since the youngest case occurred in a child 10 years of age, and the oldest in a man of 52 years. The tumor grossly presents a fairly uniform appearance. It is fairly well circumscribed, firm and whitish. One of the cases reported by Bailey was soft and red. Histologically all of these neoplasms present a picture quite typical of a well differentiated fibroma or fibrosarcoma. Mitotic figures were numerous in Bailey's cases and suggested somewhat less differentiation and more activity of the tumor cells. It is striking that all of the tumors occurred on the right side and were situated in the frontal or temporal regions of the brain.

It must be assumed that the origin of these tumors is most likely from the pia, from the vascular adventitia, or from the pial sheaths that surround the cerebral blood vessels. Bailey believes that they arise from the leptomeninges or its derivatives. In his 1st case the tumor was adherent to the dura and could easily have had its origin from this structure. The remaining reported cases, including our own, disclosed no connection with the surface meninges. However, it is well known that the cerebral blood vessels are surrounded by a sheath of cells of leptomeningeal origin which have invaginated from the surface to form the perivascular spaces of Virchow-Robin. It is entirely possible that tumors may arise from these perivascular cells and thus originally have a leptomeningeal origin. Alpers, Yaskin and Grant [3] described definite proliferation and accumulation of tumor cells around the blood vessels, which they designated as "centers of growth." In these "centers of growth" the tumor cells were in direct contact with the walls of the venules, arterioles and capillaries, appearing as an integral part of the vessel wall. The authors believed they were able to trace the adult fibroblasts from the cells around the vessels. It appears to us, however, to be quite difficult to determine with certainty whether these perivascular tumor cells actually arise from the sheath of cells of leptomeningeal origin or from the fibroblasts that normally are found within the adventitia of the blood vessels. If these tumors are of leptomeningeal origin, the question may be raised as to whether one is justified in calling them fibroblastomas, in view of the controversial embryological derivation of the leptomeninges.

There remain other possibilities of origin of such fibrous tissue tumors. Typical fibroblastic tissue is often seen in degenerating tumors of neuroepithelial origin. This fibrous tissue often becomes abundant and may lead to an erroneous diagnosis of fibroblastoma if only a small amount of the tumor is removed at operation. However, the total absence of any glial elements within a tumor and the similar absence of any signs of degeneration seem sufficient to rule out such a possibility.

Occasionally the healing of a solitary brain abscess results in an invasion and deposition of fibrous tissue, often obliterating almost all signs of the previously existing inflammatory process. Mallory [2] believed his case to be of this origin. Usually, however, these healed abscesses reveal, on careful study, some signs of the original inflammatory condition.

Finally, the use of deep X-ray therapy in the treatment of gliomas often results in their replacement by fibrous tissue and in some cases has made a histological diagnosis of the tumor quite difficult. In such cases large doses of X-ray seem necessary, and sufficient time must elapse after the treatment in order to allow such a transformation of tissue structure to occur. In our case the X-ray therapy was much too recent to result in such an extensive and complete alteration of a glioma into a fibrous tissue mass.

Considering all the above possibilities, and also considering the typical arrangement of the tumor cells, their characteristic morphology, the presence of large amounts of collagen fibers within the intercellular framework of the tumor, and the total absence of glial elements within the newgrowth, we feel fairly certain that we are dealing in this case with a primary fibrous tumor which we have elected to call a fibroblastoma of the brain.

Summary

1. A case of cerebral neoplasm is reported occurring in a 10 year old white female.

2. Pathological studies of this tumor reveal it to be composed almost entirely of fibroblastic elements. We have called this tumor a primary fibroblastoma of the brain.

3. The literature dealing with this type of newgrowth is reviewed.

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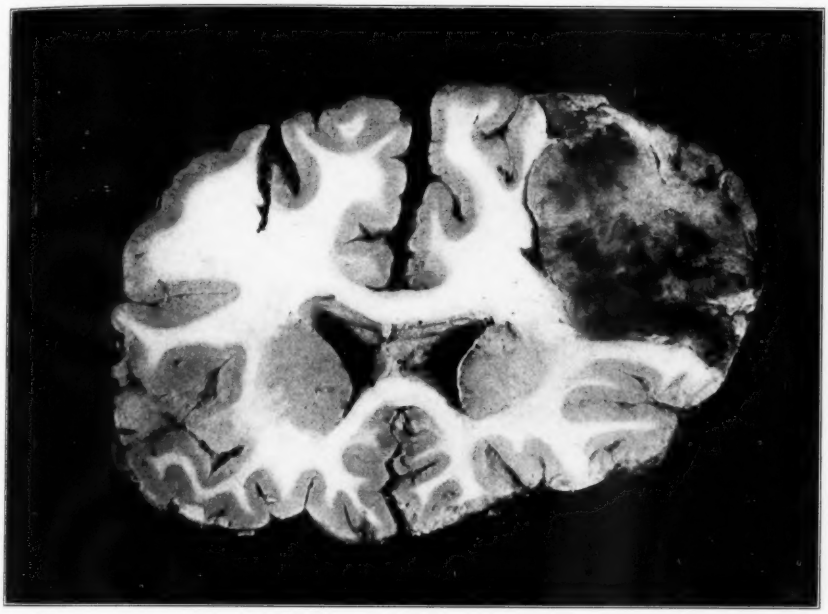
DESCRIPTION OF PLATE

PLATE 18

FIG. 1. Coronal section through the right frontal lobe of the brain. Note that the tumor is sharply demarcated from the surrounding brain tissue. The reddish streaks within the neoplasm are somewhat exaggerated in this photograph, and contrary to their appearance in the fresh specimen impress one as distinct areas of hemorrhage.

FIG. 2. Photomicrograph of a field from the interior of the tumor. Note its fibrous appearance and the paucity of cells. Azocarmine stain. × 120.

FIG. 3. Field from the center of the tumor showing the extensiveness of the reticulum and collagen fibers that make up the bulk of the intercellular substance. Perdrau's stain. × 120.



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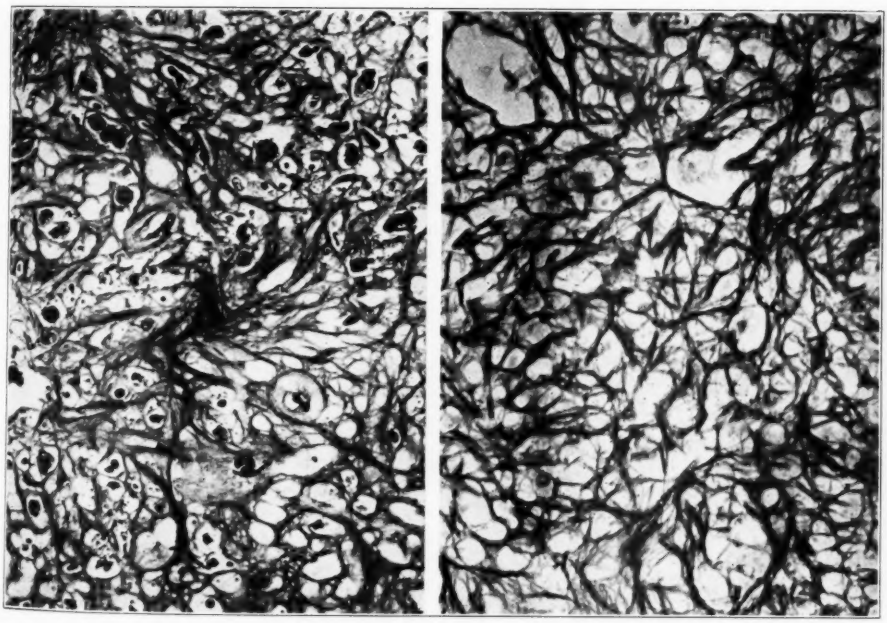

2 3

Baker and Adams Primary Fibroblastoma of Brain

BLASTOMYCOSIS OF THE HEART *

Report of Two Cases

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Publications regarding generalized blastomycosis are sufficiently numerous to make the broad features of the disease well known. From the anatomical approach it remains to define the reaction in various organs and to study the spread of the process in the body, as has been done for example in tuberculosis. Moreover, a comparison between tuberculosis and blastomycosis regarding cardiac involvement is of interest because of the similarity of the two diseases.

Two authors have dealt specifically with blastomycosis of the heart. LeCount [1] described a case of generalized blastomycosis showing miliary nodules in the epicardium. He believed that dissemination to the epicardium had occurred by retrograde extension along the lymph channels from the blastomycotic lymph nodes at the base of the heart. Hurley's [2] case, also with generalized involvement, had a sinus extending from the pericardial cavity to the body surface. One lesion extended 1.5 cm. into the wall of the greatly hypertrophied left ventricle. Two other large lesions extended through the right atrium and presented minute endocardial nodules and sinuses, which had evidently been discharging into the blood stream. The lungs contained extremely numerous, minute lesions "seeded" by the blood stream. During the patient's illness "there was evidence of cardiac disturbance, but this was a minor feature."

Several other authors have referred to cardiac blastomycosis in case reports and reviews of generalized blastomycosis. Cleary [3] found minute blastomycotic tubercles "in the myocardium and spleen in the histological examination of these organs," and one of the myocardial tubercles was shown in the illustrations of his paper. Case 1 of Coupal's series [4] showed a smooth and glistening epicardium, beneath which there was an abscess 2 by 1 cm. in the left ventricle. A few, isolated yellowish abscesses, 1 to 2 mm. in diame-

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ter, occurred on the left auricular wall. Sections showed enormous numbers of organisms. Medlar [5] wrote regarding a case: "The heart shows a small tubercle composed entirely of mononuclear leukocytes with three yeast-like bodies present." Blastomycotic infections of the pericardial cavity, apparently without involvement of the myocardium and endocardium, were reported by Churchill and Stober,[6] and by Howes and Morse.[7]

The 2 following cases of cardiac blastomycosis in generalized forms of the infection have several features in common. Pericardial blastomycosis with involvement of the right atrial musculature and endocardium, miliary pulmonary blastomycosis, and evidences of cardiac insufficiency occurred in both. Only the data bearing on the cardiac lesions, the spread of the infection to and from the heart, and the impairment of cardiac function are included in the reports.

Case Reports

Case 1. *Clinical History:* S. D., a male negro 17 years of age, developed a painless swelling below the left nipple 2 years before death. Incision yielded pus and the wound resulted in sinus formation. Later several more sinuses appeared. One year before death he developed a cough productive of yellow, blood-streaked sputum. Loss of weight occurred. Dullness and râles were present over the left lower chest. The heart was normal on physical examination. On culture *Blastomyces dermatitidis* was obtained from the pus and the sputum. Throughout the patient's course of 9 months in the hospital his temperature averaged about 38° C. Tachycardia (110 to 120 beats per minute) and tachypnea were present. An electrocardiogram made 5 weeks before death showed tachycardia, but no other abnormality. X-ray films demonstrated miliary nodules throughout both lungs, but no cardiac abnormality. During the last 2 months of life edema of the dependent parts of the body, cyanosis and increasing dyspnea were present. Two days before death the hemoglobin was 13 gm. per 100 cc. of blood (82 per cent Sahli), red blood cells 5,590,000, and leukocytes 13,500 per cmm. of blood. Clinical studies of the blood proteins were not made.

Postmortem Examination

At autopsy several ulcers with underlying abscesses were noted in the left lower chest wall. These lesions communicated with subcutaneous sinuses and with several ribs. The peritoneal cavity contained 600 cc. of cloudy fluid, and the right pleural cavity 450 cc. The left pleural cavity was obliterated by fibrous adhesions.

The pericardial sac was densely adherent to the left pleura and lung. The pericardial cavity was obliterated except for a pocket which contained pus and partially encircled the base of the heart. The enlarged mediastinal lymph nodes contained an occasional tiny nodule.

The heart could not be weighed because of the adherent pericardium and diaphragm. It appeared to be slightly enlarged, owing to dilatation of the ventricles. The left ventricle measured 1 cm. in thickness and the right ventricle 0.7 cm. Multiple sections through the myocardium showed no lesions, except in the right atrium.

A firm nodule, 2.5 cm. in diameter, projected into the atrium, reducing the diameter of the latter and compressing the auricular appendage. The surface of the nodule presented smaller elevations, also ulcers, the largest of which was 0.5 cm. in diameter and had rounded margins. The cut surface of the lesion presented yellow and gray areas. The nodule was continuous with similar tissue lining the pericardial pocket.

The cardiac valves appeared normal.

The lower lobe of the left lung (Fig. 1) contained nodules 0.5 cm. in diameter. Throughout both lungs there were miliary tubercles 1 mm. or less in diameter, with a uniform distribution similar to that seen in hematogenous miliary tuberculosis of the lungs.

The liver weighed 1400 gm. and presented the accentuated lobular pattern of chronic passive congestion. The spleen weighed 150 gm.

Microscopic Examination

Immediately beneath the inner surface of the nodule in the wall of the right atrium lie caseous areas containing blastomycetes. A crater has formed and is lined by tissue rich in these yeasts. Here the incoming blood apparently flowed over the ulcer. The nodule (Fig. 2) shows caseous areas interspersed with connective tissue and granulation tissue. Polymorphonuclear leukocytes are practically absent. Blastomycetes are numerous inside and outside giant cells of the granulation tissue.

Elastic tissue stains allow one to trace the elastic tissue of the adjacent normal endocardium into the caseous nodule. The presence of blastomycotic granulation tissue superficial to the strands of elastic tissue extending into the nodule indicates that the lesion lies in part on the original endocardial surface. At some points the endocardial elastic tissue has been destroyed. In addition to the definite ulcer already mentioned there are irregularities in the surface and projecting flaps of tissue, indicating surface erosion. Some of this may be artifact, but the presence of hyaline material lining the defects suggests that the irregularities existed during life. Some of the

crevices between trabeculae in the endocardium adjacent to the lesion contain organizing thrombi. No bacteria, including acid-fast organisms, could be stained in the lesion or thrombus.

The ramifying pericardial pocket is lined by tissue similar to that composing the nodule. The myocardium contains no blastomycotic tubercles.

The lower lobe of the left lung shows extensive fibrosis continuous with that of the pleura. Throughout both lungs tubercles are scattered which do not occur in relation to bronchi or bronchioles. Blastomycosis of the latter air passages is not noted. The hilum lymph nodes are hyperplastic. One contains an old fibrous blastomycotic nodule. Miliary tubercles in organs other than the lungs are not found. Chronic passive congestion and central necrosis of the liver are present.

Summary: Multiple draining blastomycotic sinuses in left thoracic wall; blastomycotic osteomyelitis of left ribs; obliteration of left pleural cavity by fibrous adhesions; fibrosing pulmonary blastomycosis of left lower lobe; scarred blastomycotic tubercles in mediastinal lymph nodes; blastomycotic pericarditis; blastomycotic tubercle in wall of left atrium with extension through endocardium; disseminated blastomycotic tubercles in both lungs; blastomycotic subdiaphragmatic abscess; dilatation of cardiac ventricles; chronic passive congestion of liver; hydrothorax, right (450 cc.); ascites (600 cc.); and hyperplasia of femur marrow.

CASE 2. *Clinical History:* R. H., a male negro 24 years of age, developed a subcutaneous abscess between the shoulder blades 13 months before death. This was incised and yielded bloody pus from which *Blastomyces dermatitidis* was grown. Other similar abscesses formed. The course in the hospital during the last month of the patient's life was characterized by cough productive of a little mucoid material, night sweats, moderate fever, loss of weight and dyspnea. The dyspnea was a distressing symptom terminally. He had persistent tachycardia of 120 to 140 beats per minute. The cardiac impulse seemed to be in normal position. An extra-systole occurred occasionally. A faint systolic blow was heard over the entire precordium. X-ray films showed uniform mottling in both upper lobes of the lungs. Three days before death the hemoglobin was 12 gm., and the red blood cells numbered 4,460,000 per cmm. Clinical studies of blood proteins were not made.

Postmortem Examination

The abdominal cavity contained 500 cc. of clear fluid, the left pleural cavity 1650 cc., and the right pleural cavity 500 cc. The

pleural surfaces were covered with a fibrinous exudate. The right lung had many adhesions, particularly with the mediastinum and pericardium.

The parietal pericardium was thickened and adherent to the pleurae to a greater extent than normal. No firm adhesion, however, was noted between the pericardium and the sternum. The pericardial cavity was obliterated except for several accumulations of yellow pus and caseous material. The total amount of pus was about 25 cc.

Mediastinal lymph nodes showing abscesses and caseation were adherent to the pericardium, but no point of rupture from them into the pericardial cavity could be demonstrated. However, a probe could be passed from a pericardial pocket into an encapsulated mediastinal pocket.

The heart could not be weighed because of the adhesions. It was estimated to be slightly heavier than normal.

Section through the heart (Fig. 3) showed that the pericardial blastomycosis extended into the myocardium in some places. In the region of the right auricular appendage, for example, a caseous lesion 1.5 cm. in diameter extended through the atrial myocardium and presented on the endocardium with a smooth surface. Small nodules projected beyond the endocardial surface of the lesion. The cavity of the right ventricle was dilated and the wall hypertrophied, measuring 0.8 cm. in thickness. The left ventricular wall measured 1.3 cm. in thickness.

Multiple sections less than 1 cm. apart through the whole heart failed to show myocardial lesions which might have developed there primarily and not from the pericardium. The coronary arteries were surrounded and possibly compressed by the epicardial blastomycosis. The valves appeared normal.

The lungs were compressed by the pleural fluid. The right lower lobe showed old scarring. In both lungs uniformly scattered blastomycotic tubercles 1–2 mm. in diameter were noted. The liver weighed 1700 gm. The lobular markings were accentuated. The spleen weighed 300 gm.

Microscopic Examination

The lesion in the wall of the right atrium is composed of necrotic, partially liquefied tissue containing numerous blastomycetes and

comparatively few polymorphonuclear neutrophiles. The edge of the lesion shows necrosis and granulation tissue. Blastomycetes usually within giant cells are noted. Tubercle formation occurs.

The lesion extending into the endocardium consists of lymphocytic and large mononuclear cell infiltrations and some proliferating fibrous tissue. The endothelium cannot be followed across the surface, and it appears that part of the lesion was in contact with circulating blood. This appearance is not an artifact, caused possibly by the rubbing off of the free surface of the nodule, for a similar appearance is noted in the protected crevices between the muscular trabeculae. Blastomycetes occur in giant cells just beneath the surface. There is an organizing thrombus on the free surface of the lesion, close to a trabecula. No bacteria, including acid-fast organisms, could be stained in the thrombus or the underlying lesion.

Elastic tissue staining impregnates the elastic fibers in the endocardium and demonstrates that the endocardial lesion lies not only in the endocardium but on its free inner surface as well.

Smaller lesions similar to the large one are noted in the epicardium and in the original pericardial cavity. One of these comes close to a coronary vein but does not communicate with it.

Sections from the ventricles fail to show isolated miliary lesions in the myocardium.

All sections of lungs show minute tubercles containing giant cells and blastomycetes. A moderate amount of edema is noted. The left lung is atelectatic owing to the pleural fluid. The pleural exudate contains blastomycetes but no bacteria. Blastomycotic tubercles of miliary size, such as might have come from a recent dissemination of organisms in the extrapulmonic blood stream, are not seen, with the possible exception of one minute hepatic nodule which contains no blastomycetes. The liver and spleen show extreme congestion. The liver also shows central necrosis.

Summary: Generalized blastomycosis involving the lungs, pleurae, pericardium, myocardium, endocardium, mediastinal lymph nodes, bones, subcutaneous and paravertebral tissues, prostate, and left seminal vesicle; right-sided cardiac hypertrophy and dilatation; chronic passive congestion of liver and spleen; and accumulations of fluid in the peritoneal and pleural cavities.

Discussion

Consideration of the 2 cases reported here, together with those in the literature, indicates that blastomycosis may involve the heart by extension from pericardial blastomycosis, by direct miliary involvement of the cardiac musculature, or possibly by retrograde lymphatic extension from mediastinal lymph nodes. In the cases reported here the pericardium seemed to be infected from the adjacent pleurae, although extension from mediastinal nodes cannot be excluded in the 2nd case. Neither can an original colonization in the atrial myocardium be excluded in either case.

The pericardial lesions apparently extended into the myocardium of the right atrium, penetrating the endocardium and growing on the endocardial surface. Ulceration of the endocardial lesion occurred in the 1st case, producing miliary blastomycotic tubercles of the lungs. In the 2nd case it is thought that the mechanism of infection of the lungs was the same. However, organisms may have entered the lungs through the systemic veins, since there were many old blastomycotic lesions in various parts of the body.

The presence of thrombi in connection with the endocardial lesions is related to the injury of the endocardium and possibly also to the cardiac failure. They tend to occur between trabeculae and contain no organisms of any kind. They are thus unlike the thrombi of bacterial endocarditis and more like the bland mural thrombi found at autopsy in the auricle in various conditions.

The 2 cases reported here have additional interest because the blastomycotic lesions of the heart were associated with congestive heart failure. Both showed cardiac dilatation with comparatively little hypertrophy. The possibility that the edema was nutritional in type cannot be excluded, since studies of the blood proteins were unfortunately not done. However, 1 of the cases showed dependent edema, and both showed advanced chronic passive congestion of the liver in addition to accumulations of fluid in the body cavities. The exact mechanism of the production of cardiac insufficiency is not clear. The pockets of pus between the adherent pericardial layers and the pressure of blastomycotic lesions about the base of the heart with compression of veins, as in the 2nd case, may have contributed to the congestive failure.

A comparison between cardiac blastomycosis and cardiac tuberculosis reveals many features in common. In tuberculosis, endocardial masses may develop from a pericardial process, and blood-borne tubercles may form in the myocardium and endocardium. Of interest as a point of difference is the fact that in a series of cases of endocardial tuberculosis no thrombi were associated with the lesions.[8]

Cardiac blastomycosis is comparatively frequent when it is considered that we have been able to collect 9 cases and that the total reported number of cases of generalized blastomycosis with autopsy is much less than a hundred. A similar number of autopsies of cases of tuberculosis would not show such a high proportion unless many of them were instances of generalized miliary tuberculosis, in which case the percentage might be higher. The autopsied cases of blastomycosis have been instances of generalized dissemination, whereas most cases of tuberculosis coming to autopsy show pulmonary involvement and less conspicuous generalized dissemination.

Summary and Conclusions

Blastomycosis of the heart was encountered at autopsy in 2 cases of generalized infection with *Blastomyces dermatitidis*. Each showed diffuse pericardial blastomycosis, a large blastomycotic tubercle of the right atrial wall, and involvement of the corresponding endocardium. From the latter site organisms apparently entered the blood stream to produce the miliary pulmonary blastomycosis noted in both cases. Evidences of cardiac insufficiency, dependent probably on the cardiac blastomycosis, occurred in both.

Blastomycosis of the heart may also develop as part of generalized miliary blastomycosis, and possibly by retrograde lymphatic extension from the infection in mediastinal nodes.

Blastomycosis is similar to tuberculosis in respect to cardiac involvement.

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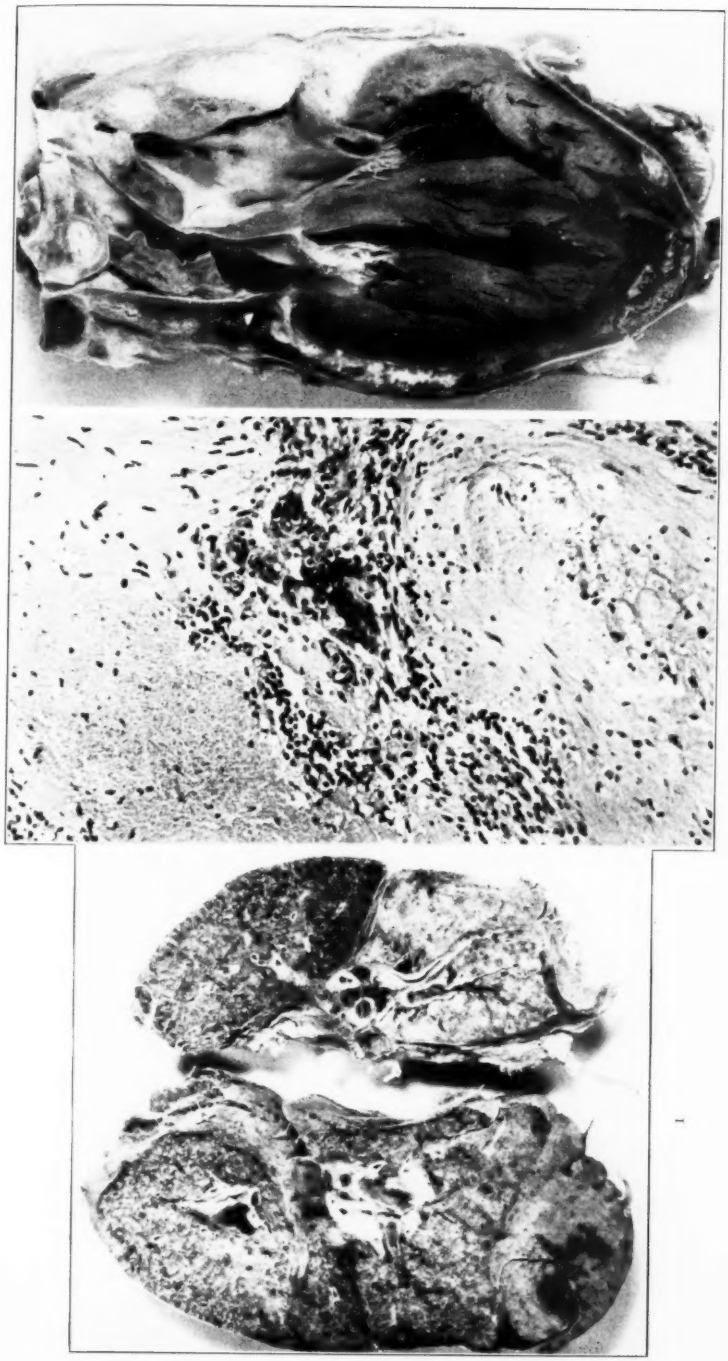
DESCRIPTION OF PLATE

PLATE 19

FIG. 1. Case 1. Miliary pulmonary blastomycosis, probably derived from dissemination of blastomycetes from the ulcerated cardiac lesion. The posterior half of each lung is shown. The process in the left lower lobe is much older than the recent hematogenous spread.

FIG. 2. Case 1. Giant cell containing blastomycetes. From center of large atrial nodule. Necrosis above and to left; fibrosis prominent elsewhere.

FIG. 3. Case 2. Blastomycosis of the heart. The caseous pericardial process extends into the right atrium above the attachment of the tricuspid valve.



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Baker and Brian Blastomycosis of Heart